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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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CARDIOVASCULAR METALLIC IMPLANTS: CORROSION, SURFACE CHARACTERIZATION, AND NICKEL LEACHING

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March 8, 2012
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FDA White Oak Conference Center
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Silver Spring, Maryland

MODERATOR: ERICA TAKAI, Ph.D.
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CDRH, FDA

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SESSION #1: CORROSION

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JACK LEMONS, Ph.D., University of Alabama at Birmingham

BRIGITTA BROTT, M.D., University of Alabama at Birmingham

SESSION #2: SURFACE CHARACTERIZATION OF NICKEL-CONTAINING ALLOYS

MATTHEW DI PRIMA, Ph.D., Office of Science and Engineering Laboratories, CDRH, FDA

DAVID SAYLOR, Ph.D., Office of Science and Engineering Laboratories , CDRH, FDA

JOHN MOSKITO, Ph.D., Evans Analytical Group

LEAD DISCUSSANTS Session 1:

MILES ALEXANDER, CardioKinetix Inc.
BRIAN BERG, Ph.D., Boston Scientific
GARY BINYAMIN, Ph.D., TriReme Medical
BRIGITTA BROTT, M.D., University of Alabama at Birmingham
KENNETH CAVANAUGH, JR., Ph.D., Office of Device Evaluation, CDRH, FDA
BRIAN CHOULES, Ph.D., Cook Medical
LAWRENCE EISELSTEIN, Ph.D., P.E., Exponent
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Bodo Gerold, Ph.D., Biotronik
WASEEM HAIDER, Ph.D., State University of New York at Buffalo
TIM JOHNSON, Cardiac Dimensions, Inc.
SASCHA KAMMER, Pfm Medical
LARRY KAY, Fort Wayne Metals
PAMELA KRAMER-BROWN, Ph.D., Abbott Vascular
JACK LEMONS, Ph.D., University of Alabama at Birmingham
GONZALO MARTINEZ, Medtronic, Inc.
EMILY McLUCAS, Ph.D., Novate Medical Ltd.
SPIRO MEGREMIS, Ph.D., American Dental Association
SRINIDHI NAGARAJA, Ph.D., FDA
Michael Nketiah, Crux Biomedical Inc.
ANDREAS ORNBERG. St. Jude Medical
JOHN PAZIENZA, OrbusNeich Medical
BRIAN ROSELAUF, Endologix
SHARI ROSENBLOOM, Ph.D., Corrosion Testing Laboratories, Inc.
VALESKA SCHROEDER, Ph.D., Johnson & Johnson
JAMES SCUTTI, P.E., Atrium Medical Corporation

CLIFF WARNER, Ph.D., W. L. Gore & Associates
TERRY WOODS, Ph.D., Office of Science and Engineering Laboratories , CDRH, FDA

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M E E T I N G

(9:00 a.m.)

DR. TAKAI: Good morning, everyone. My name is Erica Takai. I am an interoffice liaison from the Office of Science and Engineering Labs.

And welcome and thank you for coming to our workshop for the Cardiovascular Metallic Implants: Corrosion, Surface Characterization, and Nickel Leaching.

Before we start, I want to make sure that we have all the people who signed up to be in Session 1 and got confirmations are actually at the table, just in case we had any administrative troubles with printing out tent cards.

Okay, so without much further ado, we'll get started.

So I'd first like to thank all of you for coming to our workshop and for sharing your expertise with us, especially on your own dime, so we're really appreciative that you're all here.

I also want to thank and acknowledge the FDA Workshop Organizing Committee, which you see up here.

The folks with the e-mail addresses are our moderators for the various sessions.

And I also want to thank Susan Monahan. She's our logistics go-to person who has made all the logistics of this workshop possible.

So before we get into the meat of things, I want to just go over

some workshop logistics because the format is a little bit atypical.

So the format of our workshop is going to be limited presentations, really just somewhere between one to three per session, and the bulk of the workshop will be moderated discussion by the moderator with the lead discussants, who are the folks sitting up here at the table.

We'll have some limited audience participation as time permits. We anticipate most of the audience participation is going to occur in the last session tomorrow.

We are going to have fairly strict time limits for discussions because we have a packed agenda, so each session is going to have a timekeeper flashing cards saying you got to move on, so hopefully you'll understand that.

In terms of ground rules for how we're going to have the discussions, we ask that the lead discussants at the table, when you want to make a comment, to put your tent card upright on its side like this so we know that you want to talk.

And before you make a comment, for the transcriptionist, if you could say your name each time before you make a comment. That would be very helpful to us.

(Audio malfunction.)

DR. LEMONS: -- basic synthetic materials, biomaterials, as we call them, reaction to the tissue, which can really not be separated and still

cannot be separated from the transfer of force, which we would call the mechanical, biomechanical because the tissue responses and what happens in vivo are interrelated.

So if we think about the interactive transfer of elements, we have had the opportunity because of the field and the evolution to be involved with metallics probably most extensively. Ceramics, today, more polymerics and many other materials that have been tested for biocompatibility.

So if we think about the elemental transfer for metallic-based substances, because of them being conductors, electrochemistry becomes applicable. So from an in vitro environment, from the beginning, late 1960s, it was decided that a valuable method would be either the potential of static or potentiodynamic polarization methods, and at least in the first years, that was correlated most extensively with tissue culture. It turned out later that it was necessary to carry those same experiments over, move the apparatus to the in vivo environment with the laboratory animal, so most of the experiments I'll describe to you were also repeated in vivo in some type of laboratory host.

The transfers were then considered, from the implant to the host, and in the last period of 35 years, we've had the opportunity to conduct a retrieval and analysis program for devices. We've looked at about 8,000 of them where there's fairly complete records.

If we think about this period, from 1970, the biomaterials for implants primarily have been the iron-based, cobalt-based, and titanium-based alloy systems. If we look at different materials, it's much broader, which is a part of our database, and a lot of those initially were nickel and cobalt and iron, but it included copper and palladium and silver. And what's critical here is, in recent times -- and I notice now I didn't include gold -- that the gold, because of price, is being replaced again in the community with the nickel and cobalt-based alloys, so we're back in corrosion testing of those type systems.

So the publications, which are multiple, are listed under our lead investigator in the '70s, Dr. Ray Buchanan; Dr. Lucas, who is now provost at our university; Chris Navenego Polland (ph.), who is now in industry; and myself. And there are a couple of hundred of those publications over time, some difficult to find because they are more than five years back.

So here is what would happen in the electrometric studies. We would then set up in a simple in vitro environment. We would set up to apply a potential or a range of potentials, and we'd basically measure current, which we could do very precisely. We would include, then, standard controls, which would always be necessary, where we could look at our data on a relative basis. We would also have a precise control of area and contact and fluid environment. The fluid environment would range from one that would need oxygenated to oxygenated, either nitrogen or oxygen bubbled through

the solution and/or simulated tissue fluids.

But when we'd include multiple specimens, we could then do mixed potential current analysis or assess galvanic effects. And then the key to this is you can calculate ion transfers per surface area, and that was done then both in the in vitro solutions, but also in the laboratory animal.

So the mechanisms of biodegradation and corrosion for these metallics have covered all of those that would exist in a classic textbook. We had general corrosion, we had pitting corrosion, crevice corrosion, stress as fatigue or fretting, and galvanic. And I'll come back to the issue of fatigue fretting and galvanic because that's where we've seen significant correlations, clinically.

From the tissues in the host and the records from them, the histology, primarily, that was complemented with optical and electron microscopy/spectroscopy, again published in the literature, primarily part per million concentrations; these days, part per billion from the tissue and blood.

So here is where it started. And you're saying why in the world is he showing me this slide? Well, for us, this was the beginning of corrosion, and if we would assess the system, this part was polycrystalline and pyrolytic carbon transferred over from cardiovascular.

This part of it was stainless steel; this would be what would be called the abutment in the system. These were manufactured in the 1960s, made available to the community. We became a part of the test

environment. It was really an exciting time because of the changes in dentistry.

Upon receipt at our university, this is the first implant received at our university for implantation. The next morning, in the pre-assessment team, I identified the possibility of features that I thought were maybe unusual, turned out that these features were cracks that extended from the surface to the base. The pyrolytic carbon was a conductor of electricity, the stainless steel was a conductor of electricity, and unintentionally those touched one another, so in the millions of implants that were placed over the next years, we saw a significant problem in that the core of steel and the carbon were connected through a feature or a crevice that resulted in a pH gradient. That resulted in a reaction which gave us ferric chloride. The ferric chloride was quite detrimental to the tissue interface.

The in vitro side of that, Dr. Buchanan's work, basically compared, then, the steel to the various area fractions of carbon. Turns out that because the area difference of contact, there was a very significant and large area of carbon and a small area of steel exposed, so that pushed us from the normal electrochemical potentials and currents that we would see to ever increasing values. By 1974 this device was removed from the commercial market.

We saw, from those received at one practice in Alabama that we did non-destructive testing, 40% of the devices were -- contained these

features, and unfortunately, it was just simply a part of manufacturing to upscale the system. That carried over to orthopedic surgery.

Because of this system being introduced in our state in the 1960s from Russia, there were extensive numbers of total hip arthroplasty placed that combined titanium-aluminum-vanadium, cobalt-chromium-molybdenum -- cobalt-chromium-molybdenum as a metallic bearing -- titanium-aluminum-vanadium.

Now, these were anchored into the tissue with the acetabular component in the bone into the capsule for a bearing and then to the femoral shaft. So we were able, then, to deal with laboratory data plus devices from 2, 8½, 12, and 20 years. We probably had a thousand devices or so eventually in the system. And you can see this is a very long time ago.

Because as we were looking at this modular connection in the device between cobalt titanium alloy, this is Number 265 of the numbers tested, this resulted in extensive evaluation of mixed potential. And if one takes a titanium alloy and the cobalt alloy that was used in that and looked at the mixed potential, you would have a slight increase. Turned out that was insignificant as long as we had a stable coupling, so therefore that became a norm and has been used millions of times since then safely. But I'll return to that comment in a moment.

Chris Navenego Polland and many others then extended this to mixed potential, and what was critical here is it was found in some of the

devices in some manufacturing that was fretting, and fretting crevice corrosion. When we have fretting crevice corrosion, we have the two potentials independently. When they're mixed, they go to a potential in common, which is the mixed potential.

If that fretting is stopped, they repassivate and we go back to the standard condition. But if that's cyclic, that results in an altered environment that changes the entire potential and corrosion network. So in the presence of fretting corrosion, this became problematic in the community and of significance.

So if we look at the examples, the tissues and cells in histology, microscopy, and spectroscopy, here's an example of five years in vivo, the tissue interface with a mixed potential system that was implanted, in this case, in dogs.

Here's an example of the electron microscopy, looking to the cells in both tissue culture and in vivo, and a classification of necrosis of cells is a function of concentration of metallic to ion.

So here's the type of a device that was implanted in a dog. It deliberately included a crevice and combined the titanium alloy and the cobalt alloy. If you then look at this tissue interface and you look at the capsule, pigments, the cellularity, the cell types and the scores, what one sees, that the controls are not greatly different than the five-year implants for those systems in the absence of fretting corrosion.

So what's happened, then, as examples of tissues and cells, is the tissue and cell interactions were classified in terms of tissue and cell changes. In general, tissue interface is evolved in structure and dimensions, and cells showed varying degrees of structural alterations, which were correlated with potential pathology. The interactions of metallics were at part per million levels at this time, and with mixed ion fraction cells in cultures showed necrosis at 375 ppm.

So our concern was that the reaction to ion in particular species in tissues is that the mixed reaction that could result from the processes of mechanical and chemical effects could be important to clinical outcome.

So if we look at the metallic debris in cell tissue host interactions, there were significant issues, not with the other mechanisms and corrosion, but with fretting wear and galvanic mechanisms and the specific debris that was generated, and where it's a mixed grouping of ion and particular products. In those, response time relationship was different, so that led us to what I often call the "ities," toxicity, hypersensitivity, and carcinogenicity.

If we look at these, our focus, for the most part, has been on toxicity/foreign body reaction. There have been issues of hypersensitivity, allergy, if you will. That, today, has returned, and although it was not a significant issue in former times in dentistry or orthopedics, it now is a significant issue as we look at some of the metallic debris products associated

with orthopedic surgery. Cancer has not been an issue, and although we have published three cases over the years where there was an association with a metallic device, there was not a cause/effect relationship that we could identify.

So if I look at what happened in the 1990s and the 2000s comparing data with orthopedic implants, the articulation in modular connections demonstrated fretting work, erosion phenomena, with unanticipated soft tissue interactions to nano dimension debris at part per billion. Some metal and metal total hip devices were the cause of this, leading to reports of pain and the necessity for revisions. I spent five days in California a few weeks ago attending meetings at the Orthopaedic Research Society and the American Academy of Orthopedic Surgeons where that was a central focus. So, once again, we're dealing with corrosion, and in my opinion, this is something that could be avoided in the systems; however, that is to be determined.

So, in summary, we must consider that millions of metallic implants are placed each year and most outcomes are as intended. There is an extremely high benefit/risk ratio. Available long-term research development and applications exist for metallic implants. Success ratios have been based in part on better understanding of implant host interactions.

Belief is, my belief, that issues I identified will lead to further enhancements for existing systems. And we have a recent experience on

endovascular stents that will be presented in follow-up by Dr. Brott. Mine was meant to be an introduction.

If you hope to contact me at some time for anything that I might do for you as a university person, I'm at jlemons@uab.edu or several other e-mails. But don't hesitate to contact me, and I'll at least provide you an opinion. Not always correct, but never in doubt.

(Laughter.)

DR. LEMONS: You know how that goes.

So I will close then, and I'm not sure how you want to follow up. I tried to get done in a hurry.

DR. TAKAI: Oh, yeah.

DR. LEMONS: Okay.

DR. TAKAI: So maybe we'll have Dr. Brott give her presentation, and then we can have questions together afterwards.

DR. BROTT: I'm going to follow along from what Jack just talked to us about.

I have also a conflict of interest statement. I'm a co-founder of a university spin-off company, Endomimetics.

I'm an interventional cardiologist, and I take care of people having heart attacks and chest pain every day. And I'd like to start off this presentation with a case that happened a couple of years ago but which is emblematic of what we deal with every day as clinicians.

This is a case of a patient who had had bypass surgery a couple weeks prior to presentation. He developed severe chest pain and was having a heart attack. The cardiac surgeon was contacted and said that the patient was not a candidate for repeat surgery and would the interventionalist on call please take care of this. One of my colleagues was on call, he was able to open up, get a balloon down across the area of narrowing. An angiogram then reveals that the bypass graft is full of dissection and clot.

He then serially placed stents all the way from the anastomosis all the way back through the entire bypass graft to the ostium. This required use of multiple types of stents of different sizes overlapping throughout the length of this bypass graft. So at the variant anastomosis, he required a 2 mm cobalt-chromium stent that was expanded to 4 mm in the overlap section with another cobalt stent, then a 5 mm very long nitinol stent covered the bulk of the bypass graft, and then the ostium was supported open with a stainless steel stent.

This is not one isolated case. This is something that we deal with every single day as clinicians. In around 2007, several papers came out indicating that more than 50% of the drug-eluting stents were placed in off-label settings. And I'd say that our clinical practice has become more complex since then and will continue to do so. We're dealing with people who are much older, and much more highly calcified vessels are no longer really considered candidates for bypass surgery; therefore, we're implanting stents

in bifurcation settings and left mains without the benefit of a bypass graft backing that up. And there's a lot of calcification and tortuosity. And so our practice is becoming increasingly complex.

In that setting we have been, over the last several years, building on the device retrieval program that Dr. Lemons has run for more than 25 years now. We've been obtaining since, both from the UAB autopsy service, from the vascular surgery service, from cardiac transplant and other partners, and been looking at the stent/artery inactions.

So this is a typical case we obtained from autopsy. The patient had a bifurcation stent placed in his circumflex and obtuse marginal, which were overlapping stainless steel and cobalt-chromium. And he also had two different vintage stainless steel stents as well.

Our general methods were to obtain these stents, to x-ray the stented segment, and then when there was adequate tissue, digest off the tissue and send the tissue for elemental analysis. We were then able to examine the stents to look for corrosion changes using optical microscopy and scanning electron microscopy, and at times able to also perform some histologic analysis, although that was not the emphasis of this program.

And the data that I'm presenting now are summarized in two publications from Dina Halwani, who is a graduate student in our group, published in 2010.

So, again, the processing of these specimens. The specimens

were obtained, x-rayed, and then they were digested with 1 M NaOH for 24 hours. The explanted stents were analyzed and the digested tissue, when available, was sent elsewhere for elemental analysis. Our controls demonstrate that with this processing, there was very little surface alterations after undergoing the 1 M NaOH and digestion treatment.

For our initial evaluation, the UAB explanted stent specimens, there were 23 stented vessels with 39 stents. And we'll first focus on the 33, we will primarily focus on the 33 bare metal stents. But of these 33 stents, 12 showed features of corrosion. Of the six drug-eluting stents, primarily looking at their x-rays, four of these showed multiple strut fractures.

So I will show several examples, pictures, of what we saw as -- and more details of these are available, again, in these publications. However, for example, this is a nitinol stent placed in the iliac artery. They had been in place for six months, and you can see in this nitinol stent that there is diffused pitting corrosion.

More in a single coronary stent without any evidence of overlap, but as an isolated coronary stainless steel stent, there is more focal pitting corrosion associated with some abrasion damage.

From the stent, you can see that in the regions that were not corroded, that compared to the corroded regions, there is a reduction in the amount of nickel and by surface composition, suggesting a release of the nickel into the surrounding tissues.

Another example, a nitinol stent that had been placed in the iliac artery, and, again, you can see pitting and evidence of crevices.

Another example is that of a braided Elgiloy stent placed in an iliac artery; it had also been in place for three months. And you can see evidence of significant corrosion at this overlap site. In that artery, there is also a 316L stainless steel implanted in that iliac artery, and there was evidence of fretting in that location as well.

In areas of overlap, you can see overlapped fretting corrosion, and then with the adjacent Elgiloy stent, you can see that there is -- the stent, itself, looks uncorroded there. However, you can see micro-particles which, with elemental surface composition, is consistent with stainless steel.

When we look at the release of ion into the tissues, when you look at the regions of corroded versus non-corroded nitinol stent, there is, again, suggestion of release of nickel into the tissues. If you compare a normal region compared with a corroded region, there is a reduction in nickel in the surface of the nitinol stents.

We had relatively few stents that had an adequate amount of tissue, first, elemental analysis, but in those that we were able to obtain analysis, there was a significant amount of metallic ions in the surrounding tissues, and as we all discussed, this is similar to the amounts that were seen, concentrations that were seen, with orthopedic implants as well.

When we were performing this analysis, you can see that there

was significant -- we saw a lot of fretting corrosion and fractures adjacent to regions of heavy calcification. So, again, there is calcification in this region; this is magnified and you can see, again, multiple cracks and corrosion. There's a fracture adjacent to another region of calcification.

So this prompted a subsequent evaluation of vessels that were heavily calcified, and we looked at seven calcified coronary arteries involving 18 stents. Of these 18 stents, 12 of these stents had at least one fracture; nine of these were drug eluting and three of these were bare metal stents. In addition, two non-fractured bare metal stents had significant abrasion and crack-like features adjacent to the regions of calcification.

Although limited histology was performed, we did note that thrombus and extensive neointimal was found at regions associated with Types 3 or 4 fracture, so if a complete fracture with either close proximity or more distant proximity of the adjacent pieces. And this data is summarized in a publication by Dina Halwani, published in 2012, in the *Journal of Biomedical Materials Research*.

Again, looking at different examples, you can see calcification and webbing over adjacent to the regions where the stent is implanted, and there is extensive pitting corrosion and then fretting corrosion in regions adjacent to heavy calcification. And you can also see some thrombus in the coronary artery as well.

Another example, heavy calcification, complete fracture of the

vessel, of the stent, with a Type 4 fracture. This also can lead to classic deformation of the stents and adjacent fracture as well.

So what difference does this really mean from a clinical perspective? Unfortunately, we really don't know the answer. There is a suggestion that the release of the metallic ions could have an impact, clinically. In addition, the presence of corrosion could predispose a fracture and the release of debris into the surrounding tissue, creates an increased surface area for rubbing and further ion release.

We know that from work by Dr. Lemons and others, that in the orthopedic arena, these metallic ions can lead to inflammatory responses, including remote from the site of implantation. And we also know that the metallic ion levels that we have noted in our tissues are similar to that found adjacent to the orthopedic implants.

There has been limited in vitro evaluation of the effects of these metallic ions. We do know that the cytotoxicity of nickel ions from stainless steel and nitinol can affect vascular smooth muscle cell self-proliferation and vascular smooth muscle cell morphology. And this is work primarily from Taiwan, Dr. Shih.

And also work from our collaborator at UAB, Dr. Joanne Murphy-Ullrich, has noted changes in synthetic phenotype of the smooth muscle cells and change in growth factors as well.

In vivo evaluation has been very limited, as well, from a

coronary -- or a stent perspective -- this is again work from Dr. Shih in Taiwan -- that looking at rabbit studies and looking at different surface treatments of stainless steel stents, he looked at ex vivo thrombus formation as well as in vivo neointimal, and the morphologies of the more corroded of the two surface treatments is that consistent with pitting corrosion that we have seen clinically. And there was significantly more thrombus on the stent that had more -- stents that had more evidence of pitting corrosion, and there was also more neointimal proliferation at four weeks in these rabbits.

Clinically, do we know that this makes any difference? There really has been no other way to evaluate this. One, there has been an attempt to reduce the number of metallic ions released by creating diamond-like coatings onto stents, and in vitro, this had seemed to reduce the metallic ion release from stainless steel stents. However, clinical trial, this coated stent did not demonstrate any clinical reduction in restenosis.

However, one of the analyses suggested that there were significant cracks in the diamond-like coating, and therefore there was incomplete coverage, and therefore this might not have been an adequate assessment of whether reduction in the metallic ion can affect in-stent restenosis. In addition, we have the experience of gold coating of stainless steel stents, which in the past demonstrated increased risk of restenosis and stent fractures. And this has been attributed by some to be potentially associated with galvanic corrosion.

So does corrosion of stents with release of metallic ions into the tissue matter? It's really of unknown clinical significance at this time, and our goal has been, and continues to be, to look at a larger explant population to be able to correlate the presence of corrosion with the presence of restenosis and inflammation, and to perform in vivo studies to look at the effects of accelerated corrosion in animal models to assess the clinical relevance of this finding.

Thank you.

(Applause.)

DR. TAKAI: All right, I'd like to open up the floor for a few quick questions.

DR. WOODS: Terry Woods from the FDA.

Brigitta, for the stents that you analyzed, would they have been considered successful implants? Was the cause of death something unrelated to the stents and their location?

DR. BROTT: They were all-comers. So there were some that were -- a handful were sudden death, but others were placed, removed at autopsy. But others were removed because a patient required a heart transplant or some other effect, so there was a mixed bag.

DR. TAKAI: Jack.

DR. LEMONS: I would follow up on Dr. Brott's comment.

Our intent was to look at the population of non-autopsy by

sampling a population where we could obtain hundreds and hundreds of non-compromised, what would be called successful, stents. We had proposed that to the National Institutes of Health and others four times or so, but the judgment was it was not a significant issue and should not be pursued.

But we would really like to know, answer the question: What might we find or not in successful systems? And it might well be that we would prove what I think the literature is supporting, that in general, it's not an issue. But if that's the case, it's certainly quite different than what we found in this very limited sampling.

DR. BROTT: And to follow up on what Dr. Lemons just said.

What we had proposed was to look at a large sample of people who had donated their bodies for science and research, and for people who had died from all causes, and look at what happened with those stents. And so it would be for people who had not died of cardiac causes and to have a better idea. And therefore, you know, this is something that we are very still very much eager to pursue, if there were adequate funding to be able to perform this work.

DR. TAKAI: I'd like to just also add to the comments that Drs. Brott and Lemons had brought up earlier in the presentations, that we don't have a clear-cut signal as of right now in terms of the effects of corrosion and nickel ion release directly on adverse events seen in

cardiovascular devices. And I think part of the difficulty is in trying in, well, exactly what kinds of adverse events can be caused by the release of metal ions.

I think a lot of times these adverse events are not attributed to the device itself, so it may be underreported and hopefully, through further research, we can get a little better understanding of these issues.

Do folks have any other questions or comments?

DR. WARNER: So first I want to say thank you for your presentation. These studies must be extremely challenging to do and to be able to chase back all the history on these devices and what happened.

My question is what was it in the morphology that you saw in some of these cases where you say there is evidence of fretting corrosion, et cetera, that lead you to the statement that is fretting corrosion versus simply just fretting from the rubbing two stents versus each other?

DR. LEMONS: As all of us in the room realize, it's extremely difficult to separate those phenomena because the fretting results, especially in titanium alloys and others, a surface characteristic very similar. So it was usually associated with simultaneously evidence of pitting where there was not abrasive phenomena that would be in the grooves and crevices in the phenomena, you know, that we would observe.

But we could say fretting or we can say fretting corrosion, but we would see evidence of corrosion in the same stents, so therefore, that is a

reason for that terminology.

We know, in other systems that are very stable, in the presence of that interface and interface motion, the environment changes locally, and that environment, we think, pushes it over to more corrosion and that's induced by fretting phenomena.

DR. TAKAI: Do folks have any other questions?

Srinidhi.

DR. NAGARAJA: Srinidhi Nagaraja, FDA. Very nice talk, Dr. Brott.

I had a question about, in your cohort of the coronary stents, did you see, in the single stents -- well, how many were there, first of all, in the single stents?

Did you see evidence of pitting corrosion or crevice corrosion in those and was it predominantly -- in the images you were showing there, was it predominantly overlapped stents that you saw the corrosion in or was there still a significant amount in the single stents?

DR. BROTT: I don't have it on the slide. The majority of them were overlapping stents. However, we did, as in this slide here, see evidence of pitting corrosion even in isolated stents. So it was not uniquely due to overlapping stents. However, the vast majority of the stents that we did have were overlapping in some way.

DR. LEMONS: One could argue that that may have existed in

implantation, but however, that we also found unacceptable. But however, it was there and it did demonstrate, at least, the feature by scanning electron microscopy of what we would call pitting corrosion.

DR. NAGARAJA: Yeah, absolutely. In some of the work we've done in some of our non-implanted stainless steel stents, we've seen this type of morphology, and so it led us to the conclusion that maybe this here was actually something with the manufacturing process, itself, which is, I agree, unacceptable.

Did you see any -- did you have any nitinol stents, single stents that you saw corrosion in?

DR. BROTT: I would have to double check on that.

DR. NAGARAJA: Sure.

DR. LEMONS: I think the answer is, in general, no, if I'm looking at that population and thinking about it.

But once again, we've looked at a number of stents as manufactured, and we're not attempting to be critical of the manufacturer here. We're rather asking the question is there something else happening in vivo? Or in what we do in the treatment of patients?

DR. BERG: Brian Berg, Boston Scientific.

Normally, when pictures like this are presented, they're usually the worst case, in order to make the point as clear as possible.

So, one, is this indeed the worst case? Were there other cases

on this stent?

And in terms of the acceptability and unacceptability, while this isn't pretty, I would like to understand, from a clinical perspective, what about this that is unacceptable.

DR. LEMONS: I would take the position that any time we have features as you see here, that that's in mechanical flexure, albeit elastic, you're changing the induction of a crack that could lead to a fracture of the component.

DR. BERG: But there's no evidence of cracking in this, and the stress conditions are not on those particular surfaces.

DR. LEMONS: I agree with you, that's just coming from the general literature. But as we have evaluated stress corrosion cracking, the induction of the feature is really most of the process, and our concern would be it may be there.

Clearly, you're pointing out that at this side and the center, you would not expect to have a tensile component there, but we are seeing, in some systems, that even on compression or in compression side, if we have the presence of a feature, we can have the propagation.

But we did not -- although one could argue that increased surface area and change in surface in a pit, you would have a different chemistry. We don't know, especially for the titanium and cobalt alloys, if that would be critical or not because a lot of them are used in a rough

condition, quite acceptably.

DR. BERG: So what I'm hearing is that there's an increased propensity for the possibility of a fracture. And so following that through, let's say this did progress to a fracture in this particular location. Again, would there be a clinical consequence?

DR. BROTT: All we can say is what we know from the general literature, which is that if you have a Type 1 or 2 fracture, you're less likely to have a problem. So you'd have to have a Type 3 or 4 fracture, but how to -- you know, you'd have to have that in a coronary. So to be able to extrapolate the answer to your question, we don't know the answer to that.

DR. BERG: Thank you.

DR. LEMONS: Brian, I think that's a point well taken, and that's the very question that we ask also. That's precisely the question that we hope to address.

DR. BERG: I guess my main point is, while this isn't pretty, what it's showing to me, at least, in what I'm hearing, if I'm not mistaken, is that there are increased risks with this type of surface being generated in vivo. This isn't what we hope to see on these implants, and so therefore, it would be nice to improve the quality of the surface after it's been implanted, not see this type of surface, but in terms of an actual known risk, it's still at the stage of, well, there might be an increased risk or that there is an increased risk of some magnitude.

DR. LEMONS: And to put it in perspective, understanding statistics as everyone does in this room, less than a hundred out of a million is not an adequate sample.

DR. TAKAI: Brian Choules and then Gonzalo.

DR. CHOULES: My first question is, you observed many fractures, and did you look at the fracture surfaces and were you able to correlate any of those fractures with corrosion or pitting corrosion that may have initiated the fractures?

DR. LEMONS: No, but the study is actually being conducted in Cypress. One of our co-investigators went back to Cypress, and they are running simulator testing, attempting to make the correlation with what we have seen, but the answer is no, that's not completed.

DR. CHOULES: And my second question is, it sounds like you have looked at, as manufactured stents, and I'm wondering, have you looked at stents that were explanted at the same period of time that were as-manufactured, and are you able to discern between the electropolishing imperfections that commonly occur and vary in level of quality from stent to stent with these observations of pitting corrosion?

DR. LEMONS: A valid point, and the answer is no. Highly desirable. But those were not available to us or others that I would know. Although that was the case in orthopedic and dental, we had large numbers of controls from the same period, and that would be highly desirable if it

were possible to do that, but it was not something we could obtain.

DR. TAKAI: Gonzalo.

MR. MARTINEZ: Gonzalo Martinez of Medtronic.

We've had a lot of extensive experience with many, many passive and active devices, and one of the difficulties personally that I have seen is sample preservation when you deal with human explants because of regulations. It's very, very hard to be right at the implant or explant site and obtain a sample and do the analysis right away.

What I have seen, also, is that factors such as concentration of ionic species during the process and preservation in solutions that cause corrosion leave you to believe sometimes -- and this is in regards to fretting versus just erosion or mechanical abrasion or preexisting mechanical damage in the samples. It happens that as you -- things that operate or get preserved in solution should end up with corrosion over just a mechanical operation feature; that was not a problem in vivo.

So my question has to do with have you seen that, have you reproduced that? Because the clinical evidence of those explanted samples indicate to absolutely no impact in the patient, which is really the ultimate judge of corrosion.

DR. LEMONS: A valid point. I guess that's one of the advantages of having been involved in doing these type studies for a very long time: laboratory, animal and human. The precision required to process

these type specimens is really significant, requiring time. So our best opportunity there is to dedicate it to a Ph.D. student or a number of people that live their life doing that in order to control it.

You raise a point for which we do not have an answer. Could there have been particulate debris transfer that would be dissolved in the sample that would contribute to the ion concentration, and the answer is yes.

So we attempted to separate that out with ultracentrifuge and tried to process these specimens where we were not including that in the fraction. We also did a number of experiments with different solutions trying to dissolve the tissues away without transferring material, but obviously there's some. But at least, in the control solutions, that did not interfere with the data in terms of statistically changing the results.

But your point is well taken, and I agree with you totally, that if one is going to do this, it requires a high degree of precision and care because the data can be confounding, very significantly, very easily.

DR. TAKAI: Spiro.

DR. MEGREMIS: This is Spiro Megremis of the ADA.

Jack, this is kind of a follow-up of that question a little bit.

So if you -- for orthopedics, I think it's a little bit easier to look at this, especially when you're looking at a stem and a ball on top of it and you see some larger areas of fretting, and in those areas you start to -- when you look at the surface of the fretted area versus the region around it, you

start to see some large differences when you look at backscattered electrons and when you look at EDX or you try to do some type of maybe XPS or something.

And so I know it's a little more difficult to do it in these cases, but have you seen some type of large deviations in chemistry in that area on close analysis as opposed to the regions around it that indicate that you might, especially on something like stainless steel or cobalt-chrome, you start to see almost like a leaching around carbides and things like that as you continually scratch off the surface and you have to reform an oxide layer, you start to see the region around it drastically change.

DR. LEMONS: Agreed. And this is recognized, and the elemental chemistry of the surface, the elemental chemistry of the corrosion products, and the elemental chemistry of what's in the dish are all different than one another, related to precisely those factors that you listed.

But there's been fairly extensive studies on the regionalization and the transfer or not of these different metallic elements where chromium, it would be regionalized; many of the other elements and especially nickel will not necessarily and that's true of the cobalt.

But this is a new world order, and the group in your city, in Chicago, with Dr. Jacobs et al. at Rush Presbyterian, probably are in a leadership position in the world in terms of understanding those particular influences in terms of the metallurgical changes at the surface. And it's true

that there are changes, changes both in mechanical/physical properties at those interfaces with chemical properties at those interfaces.

But our concern is today, which hasn't been a concern previously, that as we have better instrumentation and we look at the distribution of nano dimension debris products, there seems to be a soft tissue reaction that's somewhat unique and different than what we would have anticipated. So that has a variety of names, so the associated and specific reactions, you know, adverse whatever, whatever.

But our concern is that a small quantity can have a very significant effect because of changing the dimensions to more than 10^{15} of these particles, you know, per unit volume. So, therefore, we have taken the position that this needs to be investigated, and it appears, though, that only a few are subject to this issue, and still, the greatest percentage of applications and uses of the devices do not demonstrate this effect.

But at least it's a large enough population in orthopedics where it resulted in a full week of discussions, two weeks ago, three weeks ago. So, therefore, it is a concern. But is it clinically relevant? To be determined. But it's certainly clinically relevant for those patients that are affected.

DR. TAKAI: Thanks.

So we're going to move on to the next objective.

All right, so for the next objective, I'm just going to show basically a compilation of the homework results where we wanted to identify

the types of corrosion testing that folks are commonly performing.

So, first, I'm going to show some demographics on the responses for the devices that we've gotten.

So, in general, a good chunk of the devices were non-coronary vascular implants, so these are things like stent grafts, endografts, and IVC filters. And the rest were equally split between coronary stents per full stents and other cardiac implants, so these include things like valves, occluders, and other coronary implants.

We did have two non-cardiovascular implant responses, which, from the numerical responses, we tended to take these out.

So when we pool all the devices and -- made of all the different alloys, when looking at the surface treatments performed, most of the devices were electropolished, either with or without some passivation processing or subsequent coating processes. There are a number of device that were only passivated or had some other proprietary surface processing methods done to them, and there are also a number of devices for which there are no surface treatments done to them after manufacturing, and notably, some of these were nitinol devices.

Of the devices for which we've gotten responses, most of them -- or sorry, a little bit more than half of them were nitinol, and the remaining balance was some kind of cobalt-chrome, so either 605 or Elgiloy, MP35N or stainless steel.

So we asked folks what types of corrosion do you do for these various devices?

First, the responses came in for -- a little bit more than half said they do galvanic corrosion for these particular devices. And of note, the no, some of these were devices where the device, itself, is only made of one metal.

For pitting and crevice corrosion, specifically, the ASTM F2129 tests, almost everybody does this particular test on all of their devices. We had two noes, but one of the noes was a non-cardiovascular device.

We then asked whether fretting was performed as part of fatigue for that device. A little bit more than half said yes.

Of note, some of these noes were people who didn't do fretting assessments at all, and 10 out of the 54 respondents said that they did testing, fretting testing, separately from fatigue.

So we also asked what other corrosion tests were performed on these various devices and -- or whether some other corrosion tests were performed. Roughly half said no other types of corrosion tests were performed other than galvanic or the F2129 testing, and the other half said yes or maybe/sometimes. And these yes/maybe/sometimes responses included other tests such as open circuit potential monitoring, explant analysis, or immersion tests where nickel leach assessments were made.

So moving on. We're going to be talking about or identifying

what kinds of -- what has been learned from this previous corrosion testing, so I'm going to show the homework first and then we'll go into more discussions.

So we asked folks to describe or identify any observed corrosion events from in vitro testing as well as any in vivo experience they might have seen. We had 15 people respond to this particular part.

And for in vitro testing, most folks said they hadn't seen any corrosion in vitro outside their F2129 testing. We had one response of corrosion, post-fatigue and overlap area, and two observations of nickel release. For in vivo corrosion, we had two yes responses, but one appeared to be due to post-explantation device handling.

So we're thinking that perhaps the relatively few observed In vivo events might be due to a low number of returned explants for analyses or, in general, underreporting to our MDR systems.

So I'm going to be showing some of the results that people have presented in terms of their corrosion testing values. First, I'll just go over some of the parameters used.

So in terms of scan rate, everybody either used 1 mV per second or the .167 or .2 mV per second per F2129. The solution used, almost everybody used PBS. A handful of people used the .9% saline or Hank's. Most of the devices for which we've gotten responses were covered or coated.

And we asked whether the devices had a crevice. Half said yes, half said no. We suspect that maybe that question wasn't quite asked correctly, so people might not have the same definition of what is a crevice and what is not.

Of note, 11 of the devices for which we got responses had both data for pre- and post-fatigue F2129 testing.

And we asked the question about in vivo corrosion again in a slightly different way, and we found that half of the folks said that they didn't analyze in vivo corrosion and half said it wasn't observed.

So, now, when we look at the pooled data for E_b or the breakdown potential, the purple line here is the median responses, and the tops and the bottoms of these bars are the minimum and maximum of all the responses that we've gotten.

We could see that the median E_b values are somewhat higher for the stainless steel and cobalt-chrome compared to the nitinol, but they're all about at the 400 mV or above range.

Of note, the nitinol and stainless steel have a larger spread from the min and max. Of the breakdown values reported, nitinol has the lowest value.

Of note, about a third to a quarter of the device responses had no breakdown of the device, and we arbitrarily put down 1300 as the no breakdown maximum because that was the highest vertex potential that was

noted.

So, in general, we did also see from the responses that the E_b on post-fatigue samples -- sorry, this graph here is for the as-manufactured device responses.

For the post-fatigue responses, we saw that the median was slightly higher -- and this is about 570, so overall the median was increased post-fatigue. For nitinol, the median increase was a little bit greater than that.

So now again, this is for as-manufactured devices. We asked folks to give us the standard deviation for the individual devices for which they were giving us results for. We could see that the range of deviations for the breakdown potentials was a lot greater in stainless steel and nitinol compared to cobalt-chrome, so cobalt-chrome tended to have tighter numbers for breakdown.

We then asked about the resting potential, and as expected, the resting potential is fairly variable across the different alloys, and even within an alloy, the range that we had reported is fairly wide.

We then asked about E_b-E_r, and, again, there are a number of devices, a third to a quarter that didn't have any breakdown. Interestingly, the E_b-E_r reported was generally above -- the medians reported were above 600 mV regardless of the alloys.

And similar to the E_b results, for post-fatigue samples, the

E_b-E_r had shifted upward for -- the median had shifted upward for nitinol, so it went from about 600 to -- the median went up to about 800 mV.

So we also asked folks about repassivation potential or E_p. Less than half of the folks reported that there was repassivation in their testing, and most who reported that they did have repassivation had values close to their resting potential value, so some negative number.

Only two folks reported that they had an E_p that was close to the E_b values or the breakdown values.

And we have little data, so it's hard to make any conclusions, but there was no glaring discernible change in the trend pre-fatigue or post-fatigue.

So we also asked folks to identify and provide values for in vivo driving forces for corrosion, and I think, as alluded earlier, there's quite a paucity of data in this area, so some of the literature that's been cited, one is an old study from Hoar and Mears. They measured the potential of various alloys, not necessarily all of those used in medical devices which included things like stainless steel and titanium.

They measured these in goats on a femoral plate and in people in a finger pin, after 71 and 90 days of implantation, and the rest potentials were in the 100-600 mV range; but the stainless steel and nickel alloys tended to be in the <300 mV range.

Of interest, in their in vitro part of their study, when they

scratched the surface of these metals, there was a transient drop in the potential that actually lasted somewhere between 1-30 minutes depending on what the alloy was.

Another study that's cited is by Pertile et al. They did open-circuit potential measurements of nitinol wires that were implanted in femoral, iliac, and abdominal arteries in six patients during a routine vascular surgery, and they measured the potentials over a 12-minute period, and they found that the potentials were about -300 mV, and they saw similar numbers when they did this experiment in vitro.

Another study is by Shih et al. They looked at nitinol and 316L stainless steel wires with a polycrystalline or amorphous oxide surface. They implanted these in the abdominal aortas of dogs and did OCP measurements over six hours, and they found that, depending on the surface treatment, it ranged from -370 to -20 for 316L and about -330 to -30 for the nitinol.

Another commonly cited value is that nerve cell conduction is in the -10 to -40 mV range.

So now we would like to have you discuss whether the corrosion testing has been predictive of in vivo corrosion based on available animal studies or patient experience that you've had.

So if folks want to share, please up your tent cards. Or if people had any questions or comments on the homework, that's acceptable as well.

Okay, Shari.

DR. ROSENBLOOM: Shari Rosenbloom, Corrosion Testing Labs.

Thank you for the summary. I'm sure that was an awful lot to have to put together.

I just wanted to ask a question or maybe make a clarification, maybe, on some of the data from the breakdown potentials that you showed of the various alloys. That one.

So I wondered whether or not -- and I can't remember from the homework, whether you had asked if these breakdowns had been verified by the formation of pits, by seeing that pits were there, because when I look at the cobalt-chromium data, a lot of times the F2129 polarization curve can be misinterpreted because there's a change in oxidation state of the cobalt that results in an increase in current density right around that 600, between 450 and 600 mV, and that could be skewing your data and also skewing your tight standard deviations that you're getting for that alloy.

DR. TAKAI: So we hadn't asked folks to confirm, to say whether or not they confirmed by visually looking for pits after their testing, so it's possible that some of these data could be from misinterpretation; we don't know.

DR. EISELSTEIN: Hi, I'm Larry Eiselstein from Exponent Failure Analysis.

I just wanted to make a comment on the Hoar and Mears paper

and some of the more recent measurements, Pertile.

The Hoar and Mears data, I think you might have been reporting that on a standard hydrogen electrode scale versus the saturated calomel electrode that I believe Pertile is. If you correct the Hoar and Mears rest potential data, it's in more reasonable agreement. I think you had to subtract about 242 mV from that. So you might want to think about doing that.

The other observation is that Hoar and Mears' data is actually really nice because it represents some long-term implantation data. I think they had data out to -- I can't remember, but over a month or maybe even three months, whereas I think it's Pertile's only had it out to minutes.

And, indeed, I think what I have seen is exposure of, for instance, nitinol to aerated in vivo-like environments. The rest potential might start out somewhere, you know, maybe -300, although that's pretty low, but it will eventually work its way up to something more reasonable like -50 or -- but not much higher than that.

And I think that's important when considering potential, you know, margin of safety over what your breakdown potential might be, so the comparison of E_b to E_r is important in understanding really what condition your sample was when you did the test.

DR. CHOULES: Brian Choules.

I just had a question about how you dealt with the censorship

of the data. Typically, the test is censored at 800 mV, but not everyone does that, and so was the reporting of censored data consistent, and how did you deal with that?

DR. TAKAI: Yeah, so we definitely had challenges with people reporting their vertex potential versus just outright saying it was a breakdown or not, so I'm guessing that's what you're asking about, how do we separate that out. So in a few cases where it was ambiguous, I just asked, you know, is this the vertex potential and you ended it, but a lot of people actually wrote, you know, what their vertex potential was and said there was no breakdown. So it was a little bit clearer.

So, you know, the data out there where it says no breakdown, those were the ones where they really were reported to have no breakdown, if that makes sense. And so the data up there are the numbers for which there was breakdown, the medians and the values and the minimums.

DR. CHOULES: Right. So there is no censored data in these at all? This represents breakdowns only?

DR. TAKAI: The graph represents breakdowns only except for the maximums, so the medians, basically, are the medians of the breakdowns.

DR. CHOULES: Okay.

DR. TAKAI: Because if it says no breakdown, I don't exactly know what value to put in order to make the median, if that makes sense, so

the median is of the ones where the values were actually reported --

DR. CHOULES: Okay.

DR. TAKAI: -- as having a breakdown.

DR. CHOULES: So if the breakdown occurred above 800 mV, then you would still put that into the calculation of the median?

DR. TAKAI: So if they said there was a breakdown above what -- you know, usually people do the vertex potential at 800 or 1 V, but if they went all the way beyond and they said that they had a breakdown, then I actually put that in into the median.

DR. CHOULES: Okay.

DR. TAKAI: Okay, Cliff.

DR. WARNER: Cliff Warner from W. L. Gore.

I wanted to follow on, on a couple things that Larry touched on.

If you go back to that Hoar and Mears paper, actually there is -- one of the things that may also be causing some of those values to look rather high is on the very short-term test where they actually inserted -- there were actually some insertions into a fingertip with a needle-like structure, they actually have a galvanic cell built into their test. They have an external stainless steel that isn't in contact with the metal that they're testing, and so there is a little bit of problem with some of that data, and we might need to, kind of, read through that a little bit.

But I also want to touch on the other comment Larry made

about the climbing of the rest potential versus the breakdown potential, and both Larry and I have published on this, and we found that, you know, both of these values do climb with time, and I think that's echoed in some of your fatigue data, that these samples have been in solution a long time, and you're seeing the breakdown potentials and the ones coming out of post-fatigue climbing.

So I don't think you can just look at a one-hour based test as a static value for the breakdown potential for a device. These values do change with time, and that's well documented in the literature.

DR. TAKAI: Okay, Srinidhi.

DR. NAGARAJA: Srinidhi Nagaraja, FDA.

I just wanted to follow up on that as well. I thought that it was interesting how E_b and E_b-E_r post-fatigue increased, and so this is an open question, what do you believe the utility of having a post-fatigue F2129 test is and if you believe the results are artifactual or real?

DR. TAKAI: Okay.

MR. KAMMER: Yes, hello. Sascha Kammer from Pfm Medical.

Just a question. Time is, for us, a very important issue. But what about surface finishing of different implants corresponding to the breakdown potentials? Is there any reference?

DR. TAKAI: We didn't break it down here into surface processing just because there are lots of variability in terms of -- you know, I

showed there were a lot of people doing electropolishing, but then there is variability within there, so we didn't really have enough *n* for each subtle difference to break it out, but we can try looking again at the larger group of, for example, electropolished versus non and see if we have enough numbers to get those sort of analyses.

DR. LEMONS: A comment: The devil is in the detail.

We learned from Dr. Mears about the importance of protecting against the galvanic effect, which is very difficult to do, but has been done subsequently.

The data really contributed a significant amount of information very early, but primarily, the alloyic conditions in that period were greatly different than what we have in many of the alloys today. So we have been dealing with a variety of cast alloys used in a final condition, especially in the cobalt and steel area. We've certainly dealt with a variety of raw conditions and a variety of surface conditions.

And this difference between passivation, repassivation, and amorphous oxide is often changed when people anodize in the titanium and titanium alloy series, and depending upon the color that one desires and the potential time relationship, you can really have an amorphous oxide, you can have a crystalline oxide, and both of those are going to react very differently -- strength fatigue.

So, therefore, the point I'm trying to make, you need a lot of

other descriptors before you can break down this data, and I think it's very valuable to look at a generalized profile, but I would agree with the comments made in the room that we'd have to add a lot of other factors to be sure that it's relevant to what we're doing today because there have been a lot of advances, you know, in processing and handling of these materials.

DR. TAKAI: Agreed.

DR. BINYAMIN: Thanks. Gary Binyamin from TriReme Medical.

I just had a quick question. I was just curious as to whether a lot of -- if there is any insight as to whether a lot of this data is coming from the development phase of devices or if they're actually coming from, you know, post-manufacturing and taking some finished devices in a sampling method?

DR. TAKAI: Based on the responses, my understanding was that these were primarily finished devices, not prototypes. These are marketed devices, yes.

Larry.

DR. EISELSTEIN: I think this was like three questions ago, but I believe somebody from the FDA had asked about what we thought about testing devices, post-fatigue testing. And I think, again, as Jack had mentioned, the devil is in the details, so maybe not always, but from my way of thinking, actually doing post-testing, you know, maybe not overlapped stents but maybe just a regular stent or a heart valve that's seen three or four

months of exposure to aerated saline or PBS is probably more like a device in vivo than a device that's just out of the package.

I also noted that in some of the graphs that were presented, particularly on the standard deviation, if I were a quality assurance guy, I'd just be frightened to death about those numbers. What I have seen, and what I suspect, is that maybe some of that is due to testing without having the sample become acclimated to the solution.

We might want to debate that or not, but certainly I haven't seen standard deviations quite as large as the largest ones you've had there on devices that have had a chance to calibrate over a long period of time.

So just to comment, yes, I think it can be useful and is likely to give you certainly more reasonable values of what E_r is likely to be in vivo after a long-term exposure and possibly -- and I think Cliff saw this, as well -- there can be a corresponding slight improvement, at least in general, on some materials with exposure, as well, with regard to E_b.

DR. LEMONS: I'd like to come back to the devil is in the detail position.

We have an opportunity, and as I have participated in many years in ASTM and ISO, I believe we have to get all the stakeholders to the table. That's an opportunity to do that, and I think if we're going to accept measurements as a part of regulatory, we really need to know what we're representing and how that testing has been conducted. And I think it's

demonstrated in the data are presented.

And, clearly, there is no reason for that large of a standard deviation in much of the testing that's done today, so you're really representing a lot of different conditions and a lot of different tests.

So there is also a lot to be gained by the way you run the corrosion test electrochemically and if you actually look at the shape of what happens in the reverse scan, that can tell you a great deal as you correlate that with pitting and other characteristics that really doesn't come from a simple measurement, it comes from the shape of the curve in the observation, essentially the oscillations that come, the minor changes that come, in the shape of the data when you analyze it in detail.

So the point I'm trying to make, it needs to go to a standard society where everyone's at the table and brings data and does a comparative analysis, wherever that happens.

DR. TAKAI: Brian.

DR. CHOULES: So there were roughly half of the breakdown potentials reported were less than 600 mV, and nitinol was less than 400 mV, so my question is there was a question regarding in vivo observations of corrosion, so were there any in vivo observations of corrosions for those breakdown potentials on the lower half of the median?

DR. TAKAI: So the folks that had the lower half of the medians, they either said they didn't look for in vivo corrosion or they left it blank or

they said they didn't see any. So this goes back to our question, again, about whether or not this testing is reflective of in vivo corrosion, and I think the unsaid answer to that is we don't know. We don't have enough data to make that correlation.

DR. LEMONS: I would come back to nitinol. A considerable experience exists in the world with regard to nitinol and the compounds associated with nitinol. And the critical issue is the finishing of nitinol, the metallurgical condition, and how it is handled. Our experience has been in orthodontics, orthopedics, and cardiovascular. There are differences in the way that these materials are processed and finished, and I believe the cardiovascular is an example of the most care that can be taken.

But if you look at the orthodontic world, what we found was that depending on the specific composition and the final steps of change in the nature of the oxide that would exist at that surface on nitinol, it totally changed the corrosion characteristics, especially in galvanic effects where we had a wire and a bracket.

So the point I'm trying to make, again, is I think we need to look at the specifics of what's happening with these particular materials and particular composition, and also whether this will include cold work or not, or a zone that hasn't been processed by cutting with a laser or not, and how that zone is removed or how that zone is affected, finally, because I think those specifics will influence corrosion.

DR. TAKAI: And I'm hoping that in our second session for surface characterization, we can go into a little bit more detail in terms of, you know, for those reasons whether we should be looking at surface characterization more carefully or not.

So I'm just going to ask a question very quickly. You know, other than the papers that we've discussed already, are there any other references in the literature that folks know about regarding in vivo driving forces for corrosion, so basically resting potentials?

I'll take -- oh, did you have a comment? Sorry.

MR. MARTINEZ: Yes, Gonzalo Martinez at Medtronic again.

I was inspired by Jack to follow up on something that is very important, and I think it is extremely optimistic to expect that the F2129 test will predict in vivo corrosion.

And the second point was that is extremely optimistic to try to correlate, breakdown potential, and even rest potentials to the performances of an alloy.

I mean, you have to understand significantly more about your system, including qualitative data like the state that was mentioned, you know, the metallurgical condition of your material. The defect density, when you look at a polarization scan, we look at meta-stable pitting, transients that may happen that are not reported really in the F2129. Yet, they may be completely -- they may be relevant or completely irrelevant. In fact, there

are publications that show there are some occlusions that really create, if you look hard enough, micro-pitting in MP35N, and they're completely irrelevant to the performance of the device.

So it's really like looking at the tail of the elephant in trying to describe the elephant when we try to do and sort of assess corrosion just on one or two or three parameters. That's my point.

DR. TAKAI: Okay, last comment.

DR. BERG: I'd like to add to that.

This is much like losing your keys in the parking lot and only looking, like, under where the streetlight is. We have a test, a very idealized F2129 that's useful, it's sort of like a tensile test, to characterize something. But the examples that were shown earlier today weren't of these types of pristine surfaces in a phosphate buffered saline; they were in vivo under abrasive conditions or under galvanic conditions. Those were the conditions under which there was increased propensity for features that looked like it might lead to a problem. So while this test tells us something, and it has some value, it's limited.

DR. TAKAI: So now I'd like to move on to discussion on the interpretation of the results and acceptance criteria for the F2129 tests.

So we asked folks what parameters do you establish acceptance criteria for and what the values are. And we see here that, interestingly, across the alloys, the median breakdown potential acceptance

criteria that people set were between 300 and 400 mV regardless of the alloy, but we do see a fairly large spread, especially with stainless steel and nitinol on what people said they're using as acceptance criteria for breakdown ranging from about 50 all the way to about close to 700 for nitinol.

And of note, three of the respondents said that they -- of nitinol devices -- didn't set an acceptance criterion in terms of the breakdown potential.

We also asked about whether folks set acceptance criteria for the resting potential, and almost nobody said that they actually set an acceptance criterion for the resting potential.

We also asked if people set an acceptance criterion for E_b-E_r, and 16 out of the 26 device responses said that there is no E_b-E_r acceptance criteria set, but for nitinol there were some that did say that they set acceptance criteria. So about six folks, and the median that they set was 600 mV, and the range was anywhere from the minimum of 200 to a maximum of 700.

Of note, regardless of what the acceptance criteria were, some folks did say that they compared the values, like the E_b/E_r or E_b-E_r to a predicate device just to see how their device is doing instead of actually setting an acceptance criterion.

Also, a few people set acceptance criteria as an average value for all the devices that they had tested, but then they would also set a

separate set of acceptance criteria that no more than one or two samples could fall below a certain minimum value.

So we also asked folks if you thought that it's appropriate to use a universal acceptance criteria across device types and alloys for those tests, and a little bit more than half said no; the rest was roughly split between yeses and I'm not sure/maybes.

Some of the common comments that we saw was that E_b-E_r might be an appropriate universal acceptance criteria, but E_r does vary quite a bit across alloys. The resting potential varies quite a bit across alloys, so the breakdown potential would need to be sufficiently high for it to pass this hurdle.

And another common comment was that the F2129 results are not correlated with in vivo outcomes, and we need to have more information and think a little bit more about the intended use and the location for which the device is going into since the potentials might not be the same depending on the location.

So I'd like to go into the discussion portion.

So the first question I have for folks is to discuss the E_b -E_r versus having E_b itself as an acceptance criterion. And to help us with this, we have a little thought experiment.

So this is a scenario that at FDA we often face. So when you're comparing it to a predicate device, when the E_b results are the same but

E_b-E_r is poor, is this acceptable? Or what if it's the reverse, the E_b is poor but E_b-E_r is better?

DR. EISELSTEIN: Hi. Larry Eiselstein from Exponent Failure Analysis.

We've thought a lot about this criterion, and I don't think there's any universal agreement between anybody, including people at our lab. However, I would like to say that whatever criteria are being used, I believe that it should be based on a statistical quality assurance type of basis. And I don't think designing to an average is that.

If you're going to say that this testing is useful and that it has value, then those values should be important, and it should be important for a manufacturer to be able to quantify that and make sure that their process is under control.

So E_b, by itself, I guess maybe the first discussion would be predicate devices. Predicate devices can be tricky for many manufacturers because if they're designing a new product in an area in which there isn't any predicate to test, it makes it a little bit difficult for them to do that testing.

And Number 2 is that if there is a device already treating that particular condition, but you have maybe a better idea or a different design that might use a different alloy, then you're comparing apples and oranges. So, for instance, somebody has a titanium device and you come in and say, well, I can do something better with nitinol or stainless steel, then you would

have a hard time beating the E_b of that titanium device; you just wouldn't be able to do it. So testing a predicate device in that case just isn't going to be very helpful.

Now, although I have seen people argue that while maybe testing a predicate device at least would provide the FDA with a knowledge that maybe you have the set of values for the predicate device and you know what those values are, and therefore you can use that sort of as a calibration to make sure we know what you're doing, but, in effect, if you're doing these tests, you're supposed to run the G5 test to make sure you're calibrated, and I believe that calibration is not against a 400 series stainless. So, supposedly, you've already done that. So I sort of discount the benefit of testing predicate devices.

So now the question is, well, should you base it on E_b or E_b-E_r? I think that's a little bit more controversial. I think Corbett was one of the first gentlemen that said, you know, I've tested enough of these and I know you can make, sort of, different materials with different E_b values, and he sort of said, well, if you're within this range of E_b's, you're maybe okay and don't need to do any more tests, but if you're below a certain level, then I've got to do a lot more tests, but he doesn't tell you how many to do.

So I think you could potentially base a standard on E_b, and if you were to read between the lines of Corbett's original paper, he'd say, you know, if you're below 300, maybe you should just stop and think about doing

something else.

And I think probably a lot of us in this room would agree with that, but -- and on that basis you might, for instance, want to set a quality assurance that as long as you're above an E_b of 300 and you are 99% confident of a 95% confidence level, you know, that might be an acceptable goal, but you would have to do enough tests to show that.

I actually think that it makes a lot more sense to do the measurement on E_b-E_r because that's really the margin of safety you have against pitting in vivo. Now, the argument was, well, E_b changes over time. Well, that's certainly true, and that's why I think that the criteria ideally ought to be, well, we measure E_b-E_r, we do it on a statistically valid sample, we do those on samples that have a calibrated and an aerated in-vivo-like environment for a month or two. So, for instance, testing, you know, post-fatigue tested samples. And there you'll see much less scatter than you saw before. And the E_r will have had a chance to, you know, stabilize.

And really, it's that difference. It's, again, I think somebody had mentioned it's sort of like yield strength, right, so you know that your device has an E_b of a certain value, and for titanium that might be 2,000 mV, and for a nitinol device it might be 600 mV. But if both of them are being exposed to a very low stress, it doesn't really matter. It's the difference between the rest potential and the breakdown potential that's important.

And I know I've taken up more than my time, so I'll be quiet.

DR. TAKAI: Thank you.

So Brian, Cliff, and then Shari.

Sorry.

DR. WARNER: Cliff Warner, W. L. Gore.

Just a quick comment, I don't want it to be misconstrued from Larry's statement, that E_b does change with time, but what we've seen and published on this, that it changes commensurately with E_r, and so actually, that leaves a little credence to the use of E_b-E_r being a more time-stable value rather than hitting one value in a moving target.

DR. ROSENBLOOM: Shari Rosenbloom from Corrosion Testing Labs again.

So to comment on what you were saying and take a look at this, first of all, Rick Corbett was the founder of Corrosion Testing Labs, and you mentioned him, so I thought maybe I'd clarify what his position was and where he came to, how he came to the 600 mV criteria, which was an E_b criteria.

What Rick looked at was that -- you're right, that he said that if something is less than 300 mV as -- for E_b, that that was considered unacceptable. He wasn't comfortable with that, and we're not particularly comfortable with that.

Between 300 and 600 mV, he felt that the material was, he considered, marginal. That's not really maybe the right word, but that it

warranted further testing and examination to understand what was going on and determine whether or not that it would be acceptable.

And then above 600 mV, he drew a line there, and said that if you could demonstrate that the breakdown potential was above 600 mV consistently, that that was acceptable.

And he came up with that based on the Hoar and Mears data and probably looking at the Shih data as well, and trying to pick a conservative number that he felt could be applied universally across all devices and all alloys, and he felt that that was conservative and that we would be safe with that.

So from that perspective, you know, looking at E_b-E_r is another valid way of doing it. The difficulty that you get into, and the thing that I think we always have to think about with any acceptance criteria for F2129 is how is the device going to be used, and is it possible that it's going to be used in contact with another device, or what are the things that are going to happen to this device because if you look at -- well, we had an example recently.

We've seen galvanic couples that have actually driven the nitinol in the couple to pitting, so this might have been a nitinol that had an E_b on the lower end of the spectrum, but maybe, you know, around 300 mV, somewhere in there. And we've seen the galvanic couple that has been created that actually caused the nitinol to pit in that galvanic test.

So knowing that that kind of thing can happen, I think you have to look really carefully at how this device is going to be used and whether or not it could come in contact with another device or whether it is going to be fretted or what's going to happen to it and think very carefully about your E_b, especially if you're looking in that what we consider marginal range of 300 to 600, regardless of what the E_b-E_r is.

DR. TAKAI: Cliff and Gonzalo.

DR. WARNER: I'll pass.

DR. TAKAI: Okay.

MR. MARTINEZ: Gonzalo again of Medtronic.

We actually have debated this for years. I remember one of the first things I did 21 years ago when we started working for Medtronic in corrosion was that exactly. And I came up with a polarization curve, cyclic polarization curve, and my boss asked me if that was acceptable, and I said no. I was doing component testing, and he told me we've been using those devices, that material, for many, many years. That is the problem with this acceptance criterion.

So we debated this internally, and what we came up with is basically we don't believe rigorous, normative acceptance criteria is a good idea. I know the extremes that are very good and very bad on breakdown potentials. I like the E_b-E_r, but I always want to know the thermodynamic potential as well.

The issue is this: I mean, if corrosion, it just -- an effect that interacts with other effects, like mechanical factors, but the ultimate passing criteria determines an acceptance criteria is actually the effect on the patient, the risk. There's a very good reason why, if you read the ASTM standards, and I was using ASTM F746 for many years, they mention the word corrosion susceptibility. Doesn't mention the word corrosion risk -- excuse me, corrosion life prediction or anything like it because you can't do that.

So unless it's a guideline, we think it's a bad idea to put acceptance criteria. For example, magnesium stents, what is the breakdown potential of a bio-absorbable stent, right? You make all those materials fail the ASTM F2129, so nothing is acceptable then, right? So that is a problem.

DR. TAKAI: Valeska and then Spiro.

DR. SCHROEDER: I wanted to make a comment related to that about using this test with an acceptance criterion versus using it as a development tool. And I think, for people who have been working in making medical devices, you can see a lot of value in using this as a development tool, but that idea of if it's below 300, maybe you should go back and look and see what you could change in your process to bring yourself up. But then a true acceptance criterion in relation to the in vivo condition, I do think that that's lacking, so I see a lot of value in the development aspect of the test.

A comment, going back to the E_b-E_r versus E_b, I think it's interesting that 23 out of 26 respondents didn't have an acceptance criterion

relative to E_r, and I think that's because we don't have a lot of knowledge about what is correct, but then people do feel like they can step up and have an E_b-E_r acceptance criterion. I've found that E_r is more sensitive to test condition; there's more, kind of, day-to-day variation in that result.

And so I'm more inclined to the E_b having more value than the E_b-E_r even though I understand that from a risk perspective -- and if you have the true E_r in vivo, the value of that difference, I understand that. But from a test perspective and applying an acceptance criterion, I feel E_b has more value.

DR. MEGREMIS: Yeah, I'm just going to echo a lot of what was said here by saying that it's a very small picture in a bigger picture in that it doesn't tell you a whole lot about the tenacity of the oxide and what happens when you scratch it and what happens when you put something next to it.

But it's a very valuable screening tool, and I think the problem comes about when you try to put some numbers and say this is a bottom line or -- and I think we've talked about this a lot in the ASTM working group about that there was a lot of pressure for Rick to put some bottom line numbers there. Yeah.

And I give the reason for that, and it helps to have some numbers that you can use and go hey, this is unacceptable or acceptable. But then when you try to kind of look at that blindly or in a regulatory -- or I think Brian has talked a lot about this, is when you start trying to develop

something for -- and maybe for different countries, et cetera, and they go hey, we're not going to accept this if it's under a certain number or if your E_b-E_r is too small, et cetera, that's when it gets into a problem because you could probably look at some materials that have relatively high E_b's but the oxide isn't a very tenacious oxide or it doesn't do what were, under certain conditions which, you know, phosphate buffered solution is not all that predictive, sometimes, of in vivo conditions.

So you're talking about something that's in a very basic solution, not very complicated, no proteins. And so I guess I'm just echoing what a lot of other people said here, which is probably not -- it would be nice if we could come up with a number, but I don't know if that's going to happen.

DR. TAKAI: Okay, so I'm hoping that people also, as they speak, keep in mind also the general question of whether or not a universal acceptance criterion in addition to this discussion of E_b versus E_b-E_r, I think some people have already alluded to that, but if you could also give your comments on that as well.

So maybe we'll go to Cliff and then -- I'm sorry, the gentleman next to Brian Berg and then back to Larry and then Ken.

DR. WARNER: Cliff Warner from Gore.

Just to touch base on, if you go back to the question of E_r and reproducibility, if you go back to the round robin for ASTM F2129, we actually

measure the test method reproducibility, and kind of surprisingly, E_r is much more reproducible across the foreign material sets that we looked at than even the E_b numbers were.

So I don't disagree there's a lot of nuances with E_r and that number can -- you can do some things in the tests that will cause that value to vary significantly if you do some things in the test incorrectly, as it's stated in the methodology today. But all in all, it is a fairly reproducible number with consistent material flowing into that test method.

And so I think, in terms of the question of -- you know, one of the questions I ask, in my mind, when we start talking about E_b-E_r versus E_b alone in terms of is this a more useful value across material sets? In a certain sense, when you go back to looking at literature values, you know, in where people have directly correlated the phenomena in the in vitro test to, let's say, a real-world corrosion value, it is a primary like E_b-E_r is the one that has the most beautiful 99% confidence kind of relationship. And, you know, go back to Wilde and Williams' work and you'll find that.

And in a certain sense, you can look at that almost as normalization coming out of this, and it takes out some of that, in my mind, some of the variation, the input material, into this methodology.

DR. EISELSTEIN: I'd like to sort of echo some of the comments that were made by Medtronic and other people, as well, in that I think an acceptance criteria for a device, whether it's E_b or E_r, and I think Shari has

also mentioned, you know, well, gee, what if you have -- what's the end application if you have galvanic issues, you know, there might be something else.

I think really what we heard starting out with this meeting is that -- at least, my feeling is that the majority of any in vivo problems with the millions of people that have implants is probably more predicated on fretting and wear-related issues, overlapped stents, or fatigued fracture of stents that might expose fresh fracture surfaces that might corrode. So we're really sort of arranging chairs on the Titanic as they're going down in that it's maybe not all that important because there doesn't seem to be any really glaring issue with regards to the alloys that have been produced and implanted so far, in general.

Therefore, whether you base it on E_b or E_b-E_r -- and I, from a purist point of view, I think really, if you were to come up with a criteria, it really has to sort of be based on E_b-E_r, and that if you're going to do that, then the E_r, in order to have it -- in E_b, as well -- to have it be reflective of what's happening in vivo, you probably just shouldn't test it in its electropolished condition. You might want to do that, but you might want to test it after it has been exposed to an environment for a certain period of time.

Shari made a good point. If you've concerned about overlapping stents and galvanic couple related issues, then you really need to

know what your E_b is because it isn't going to be the E_r of that stent anymore that's important; it's really how much is it being galvanized to a different potential and is that couple that it's going to be exposed to going to get it close to where its effective E_b-E_r might be so small that you could have a corrosion problem?

DR. CAVANAUGH: Hi, Ken Cavanaugh.

Well, I guess part of my ongoing efforts to make meetings all about what they can do for me, just thinking about in terms of regardless of where the discussion goes with whether there is a way to identify a value that may be appropriate as an acceptance criterion, I can just say from the regulatory standpoint, sometimes that can't be done.

What oftentimes we look for and perhaps folks in industry have seen questions like this from us before, it would be just with regards to whatever results or whatever acceptance criteria you set for a test, please tell us something about why you're okay with that result or that acceptance criteria. Were there other conditions of expected use that influenced it, other evidence from past clinical history, from the development process? Maybe there were previous versions of the device involving data that we don't typically see in submissions that may be important, showing some improvement over that.

Maybe as part of the discussion today, hearing about what types of factors may be appropriate -- and I think we already touched on that,

but maybe delineating that or consolidating it a little bit may be helpful just to think about here are the types of considerations that should go into figuring out whether a test was successful or not.

We've heard a lot about, well, the metals that we've mainly been talking about here do seem to have a good history of clinical use, but again, from our standpoint here, we may not know about all the various tests that were done beforehand involving tests that had disastrous results and just hearing about the role of this test, learning more about that and thinking about when we finally got to this result, something that we're satisfied going forward with for clinical use, here's why we're okay with it; I think hearing something about those factors may be helpful in further informing the discussion.

Thank you.

DR. ROSENBLOOM: I guess what I'm hearing and, you know, what we've talked about and thought about a lot is, what we're trying to do here is to come up with possibly a universal acceptance criterion or at least some kind of an acceptance criterion that could be fairly simply applied to this test, and the problem is that it's not a simple problem. It's a really complicated problem. This is one test that's done in vivo, doing our best to simulate, you know, in vivo conditions, but it's an in vitro test. Did I say in vivo before? In vitro test.

And without having, really having, the in vivo data of

performance to correlate it with, it becomes very, very difficult to come up with a single or even a couple of truly universal criteria. And I guess that's getting back to where Rick came up with the 600 mV because he felt that it was so conservative and he felt that it really would be valid, as best as he at the time could figure.

And, hopefully, what this meeting is designed to do is to bring all of us together and get all of this data all in one place and just start to look at some of that in vivo performance and see if we can't make some of those connections. But it is a very complicated problem and so trying and come up with one, just a number that we're going to apply and say this is it, unless it's very conservative, it's going to be very difficult to do.

DR. TAKAI: So I wanted to summarize a little bit about what I've heard so far.

So in terms of acceptance criteria, it seems like some people feel that because of the nature of the tests and the variabilities, that it may not be as appropriate to have a hard number for acceptance criteria, whereas some others feel that perhaps E_b or E_b-E_r is perhaps appropriate for at least a baseline minimum, possibly as a screening tool to say, well, below which you might need to reconsider your device.

So I think what we also don't know, as Shari has just mentioned, is where the line in the sand to draw is because from a regulatory standpoint, as Ken has also mentioned, you know, we'll look at what the

justifications are for the acceptance criteria that folks set for this test for which the standard has no acceptance criteria, but we want to get a more granular input on at what point do folks say okay, well, this number is really too low either for E_b or E_b-E_r and why folks think that way about these particular numbers, if people can comment.

DR. CHOULES: Brian Choules.

The truth is we don't have a direct correlation between E_b or E_b-E_r and clinical results. I think what we do know is we haven't observed a significant corrosion issue with the devices out there today. I mean, there's been a few reports of minor observations of corrosion, but no significant problems. There are data and people are setting the acceptance criteria that are well below the suggested values by Corbett.

I mean, right here, values below 100 mV that are acceptable, and yet we're still not seeing a significant clinical issue of any clinical issue. Even the observations of corrosion haven't been linked with fracture, which to me is the most important thing. If you fracture the stent, then you have an issue. If you just have some minor observations of corrosion, we don't really have a significant issue.

DR. TAKAI: So, hopefully, I don't get in trouble for saying this, but from a functional standpoint, I think oftentimes we do look at the Corbett paper and the acceptance criteria that's been outlined. I think Shari has mentioned, you know, the 300 number; below 300 is perhaps not acceptable,

300-600 mV range being marginal. But at the same time, I think it's fair to say that we also look at other tests in addition to F2129, so either other corrosion tests, nickel leach tests, or other kinds of tests.

So I think what we're trying to do here is to figure out, well, you know, is there this sort of gray zone below which we need to be worried about other sort of assessments in addition to F2129, or are there sort of magic numbers above which, well, we don't have to worry as much about other tests?

I think, generally, what I've also heard is that F2129 is a screening test. It only will give you a rough estimate for, perhaps, some corrosion properties, and it's not the be all and end all, so it probably shouldn't be used as the one and only test.

Perhaps people could comment on that.

DR. BERG: Brian Berg.

One comment about the breakdown, E_b or E_b-E_r. More on the E_b is that, you know, we're talking primarily about these three particular alloys, and maybe for these three particular alloys, setting a number might be appropriate. But even then, you have to be very careful that you're properly interpreting the results of this to show that there is pitting, particularly from the cobalt based alloys.

But as we get into future alloys, we know that the rest potentials of these other metals that may be used and other oxides that

result on the surface may have different rest potentials, may have different interactions in the body. So let's not set a number based on a few samples and assume that that's appropriate for all future alloys.

MR. KAMMER: Sascha Kammer from Pfm Medical.

Perhaps general comments. From my own experience, I was faced with this kind of testing beginning 2010, so before I had the experience with impedance measurements of micro-neural implants, so create -- et cetera, what's well known.

This was a new kind of testing for me. I've started with, and so how to begin with that, okay. You read the standard, you try to follow the standard, you read a lot of papers, of course, and I think a lot of people here have a lot of experience over the years, and you try to follow, you try to have contacts, and then you try to find -- criteria. You have no criteria to understand that.

And then you find some papers, perhaps, to cover the paper, and you do a lot of tests with different materials to have some feeling, which way can we go, what will be the result? You test wires, you test structures, perhaps stents or occluders or something like that, and then you have some results. And it seems to me it's a kind of hunting to high E_b values to show, okay, the product is fine, it's according to some papers, and so we have it.

But I think the most important thing is that we have, of course, a safe, very safe, implant that we bring to the patient for a lot of years most

times. And it's very hard then, to follow the line, to find some way to say okay, now it is safe, now I can sleep very well because I have a very safe implant. And you're talking about E_b, E_b-E_r, later on E_p and to different other word use, and it's quite confusing which way to go, okay. Therefore, we have this session here, that's clear.

But from an engineering point of view, it's very good to have a guideline, very strict guideline, to follow or otherwise, there are no accidents which -- because you have a lot of fields, a lot of very different implants, and you have to define it for the very specific field you use this kind of implant.

So this was just a statement for this.

DR. LEMONS: I'll start.

From long-term experience, looking at surgical implants in the laboratory, the materials, biomaterials, and then the in vivo circumstances, I believe we can say with confidence that the initial testing in vitro and the initial corrosion testing in vitro under passive conditions, under the circumstances of the environment and the solution that's used, is a meaningful relationship and has some value in terms of the development process.

But I would point out to you that what experience has shown us is you need eventually to look at the outcome of the devices in vivo and ask the question what might have changed? And I take the point here that we have seen a number of examples related to galvanic conditions where the

corrosion product at the contiguous interface is adequately hard and adequately stable where it separates the components from continued galvanic reaction and they remain stable in vivo.

But I would point out to you that these products at the interface in vivo are uniquely different than phosphate buffered saline. We get complex tetrachlorides, we get a variety of environments. So the point I'm trying to make is we need to assess, as best possible, the information from what we have been able to validate, that it represents what is happening and then ask the question how does one minimize that effect in vivo?

And that comes in from a different set of tests, not a passive test where you have a static condition in a phosphate buffered saline. Now, I think that's a very important number and should be collected, but it's only a part of the equation. And what we're now finding, in other devices, is that you have to work backwards in a way and simulate what has been found in order to take a corrective action.

DR. TAKAI: Larry, then -- oh.

DR. BERG: Brian Berg.

I'd like to add to that and use a language of I think we're looking in the wrong doorway of acceptance. I think what we should be doing is doing this comparison between what we're measuring on the bench, what we're seeing in the field, and if we're seeing things in the field that we don't

like, can we replicate them on the bench? We should find out what's unacceptable rather than looking for what is acceptable because you can never prove the nonexistence of a possible harm, but you can reproduce things that have been harmful.

DR. TAKAI: Sepehr.

DR. FARIABI: I found the corrosion testing is a very useful tool for the -- as was mentioned before, as a development tool, manufacturing process controls. We've been using almost more than a hundred tests just to develop a new process for -- passivation, and we have referring to as well below 300 for E_b and E_b-E_r, because it's 600.

But the issue is, as you get to more complex geometries, you are getting into, like -- like 1,000 -- with 120 -- for braided and all of that. It becomes very complicated, and the inclusions in the raw material are causing most of the corrosion failure. I mean, I've seen the inclusion of titanium carbides and oxides. Those are going to create some nickel exposure and that's going to fail at -- and then you fail at 200, for instance, even though you have 300, but you can pass for one lot, 800, most of the time; then you get another lot, because of raw material changes, you have a breakdown.

What do you do in this case? I mean, is just having a solid criteria is -- you're setting yourself to fail, eventually, in some lots. However, it's a great tool to have as part of the process development and controlling the manufacturing. Contamination is a big issue sometimes, and

contaminations -- those are affecting your corrosion data.

DR. EISELSTEIN: Okay. Larry Eiselstein, Exponent, again.

I'm just going to sort of echo some of these other things.

I think once I was at a talk that Jack gave where he was showing an example -- and I might have this confused with someone else, but an example of a 70-year-old World War I veteran that had a piece of steel stuck in him from that time period, and it looked like he was doing fine for 70 years.

Now, obviously, that's iron, not nickel, but again, I think it gets to the point that Brian had brought up as well which is that we have not seen, I think, any examples of -- we have worries and concerns but no, I think, substantial evidence that there has ever been a significant issue with regard to corrosion or corrosion induced failures. Certainly mechanically induced failures, yes; we've had fatigue fractures. Why is that? It has to do with how the biomechanics have maybe been under-representing the stresses that are on the component.

Fretting and wear? Yes, that's the case. But so you could look at those examples, say, where you have fretting and wear, which obviously has produced metal, small metal, particles; probably significant increases in surface area; perhaps increased nickel/cobalt release. And even there, in those situations, I'm not sure that I've heard that that has produced any significant health consequence.

Now, actually, I was going to comment on the talk earlier because I was wondering whether or not anybody has looked at the amount of restenosis that occurs, and this might be hard to do, say, for instance, where you have overlapped stents and then say, well, that's a lot higher than having just individual stents, and then you could say, well, maybe it had to do with the abrasion and wear as a result of either the galvanic or the wear there. So that might be one way to get to that.

The next point that was brought up is that with regards to a criteria for acceptance, I think the point was made, and it's a valid one, that for a manufacturing quality assurance point of view, it's sort of good to keep track of what E_b and E_r are as you're manufacturing your device because it allows you to see whether your process is under control. And that's a little bit different, I think, than what we're talking about.

But, again, I would agree with that because if you change your vendor and he provides you something with a much higher inclusion content and you have an inclusion sitting of the surface of your device, it's going to change the value of E_b.

And then the other comment that you had made, are there other tests that are useful, and I certainly think that the nickel release test or metal ion release test, under some circumstances, might be quite helpful to decide, at least, you know, what level of metal ion release you're having from your device.

DR. TAKAI: So I hope folks keep this discussion about having acceptance criteria versus having just the line in the sand when we have our discussion tomorrow afternoon on what kinds of testing to consider and when.

So the next question I wanted to ask you folks is to discuss the significance of the repassivation potential, when you might want to look at this a little bit more carefully and why.

DR. LEMONS: Could I follow up before going forward?

Making a point about the soldier and 60 years in vivo, the intent of that discussion is we had comparative analysis between 304 stainless steel and 316 stainless steel and vanadium steel. And although some were tolerated, in general when you have significant corrosion, you can have a fistula. But, in general, the answer is biology is amazingly tolerant and especially of the 304 and 316 steels.

We have this question of n=1 and what does it tell us, and it in some cases is represented 10^6. So we have a few examples where one observation has led to multiple observations that has shown us that irradiation of polyethylene in air was not a thing that should be done at the levels that were happening at the time.

We have that in metallurgy also in a number of cases, but in general, n=1 or n=10, it really represented an unusual condition, unanticipated in the field, like heating an inductive furnace that changed the

microstructure, which changed the basic properties, which changed the corrosion, which contains the fracture. But that was a simple correction that came from a small number of observations and never reached large numbers.

But I think the key to all of this is you have to have all of the stakeholders at the table. You cannot make these decisions from a few observations, and you have to have a consensus opinion. Otherwise, you're spending millions of dollars correcting something that really isn't broken. And we've seen that multiply, that very often there's a reaction and activity to correct something, and in the interest of the community at large, that really should not have happened. But we've seen the opposite, also, where it should've happened earlier, and that comes from the basic data that are presenting.

DR. TAKAI: So I'm hoping that people can also discuss the protection potential. I know the F2129 group has a lot of debate right now on whether or not you need to measure E_p. Maybe somebody in the group can briefly summarize the debate?

Brian, please.

DR. CHOULES: So there is plenty of evidence that acceptable implants do not repassivate at potentials that, you know -- really repassivate at all. There is very inconsistent repassivation with these perfectly acceptable implants, and I think the data that we collected here agrees with that. And part of the problem is that we're driving potentials very high relative to what

the in vivo potential is going to be, and then when you try to repassivate that, it's more difficult to do that as the pits grow to be very large.

And so, essentially, ASTM is discussing how to deal with this and whether or not we should be comparing it or have an acceptance criterion for it at all, because many regulatory bodies, once they see that you measure a value, you need to have an acceptance criterion for it. And so we're discussing that, and I think we're at a point where we agree that the value is meaningless when you have a breakdown potential that is deemed acceptable. But when your breakdown potential is questionable, then protection potential may become more relevant.

DR. TAKAI: And, of course, judging from our earlier discussion, we can't really figure out what is the good breakdown potential or acceptable breakdown potential. We're having difficulties in even drawing a line in the sand. So I don't know, folks, have -- oh, okay.

DR. LEMONS: When it was called the National Bureau of Standards, Anna Fraker conducted a series of tests on the kinetics of repassivation, which is very critical, I think, to understanding the processes of particulation.

That was followed up by Anne Van Arden (ph.) under the NIST handle, and those data, I think, were quite convincing that the kinetics of that repassivation and the change in the electrochemical potential were very different under different use conditions.

So the point I hope to make is that if one is going to look at the magnitude of those numbers, you really need to be sure that it's representing the in vivo environment conditions of use of that particular device because it was very, very different depending upon the application.

DR. TAKAI: Valeska, then Larry.

DR. SCHROEDER: Valeska Schroeder, Johnson & Johnson.

As far as passivation potential, I guess what I've seen is that that seems less device-dependent, and so you're getting a value that's reflective of the material but not necessarily of the device, so I see less value there.

You're also giving up information about your pit location, that if you can stop the test right at breakdown, you can determine where the pit has formed, and that might tell you something about either your manufacturing process, your device design, or something that's that sensitive, and I see a lot more value in the test usually in that form, and we actually run the test double sometimes so that we can get that data. And then for to be able to follow F2129, we run it with the passivation potential taken.

DR. EISELSTEIN: I guess there are a couple comments I'd like to make; some of them are fairly obvious.

But I think one of your questions was when does repassivation potential perhaps become important in a medical device, and I think one of the obvious things would be, well, where it's used in a potential fretting or

wearing type of environment. So, for instance, if you had a woven or overlapped wire stent design made out of, say, nitinol, that might predispose that particular device to significant wear and fretting related corrosion.

On the other hand -- and I haven't done it, maybe somebody else has, but I'm assuming that titanium, for instance, probably has a pretty good repassivation potential. I don't know that for a fact, but I would assume it would. And, obviously, it doesn't do well in fretting conditions either. So maybe repassivation potential isn't a very good example because you can use titanium, which has a pretty high breakdown potential. I'm thinking it probably has a pretty good repassivation potential in kinetics, but it does very poorly in a fretting type of environment. On that basis, I'd say that, you know, maybe it doesn't make sense to do that.

The other item is that I think, obviously F2129 was a standard put together by a committee, and we all know what that gets you. And it's maybe not the best -- maybe it's not the best standard to measure repassivation potential. There are other ways to do that, and I forget which ASTM number it is, but there's one that I did once or twice, it's very painful but you can do it, where you step up, and if nothing happens, you then step up farther, and then when you finally get breakdown, you then come back down. And you can -- which one?

MR. MARTINEZ: ASTM 746.

DR. EISELSTEIN: Yeah, 746.

And that one gets you a better chance to get a true passivation, repassivation potential, but it is sort of time consuming.

DR. TAKAI: I'll just throw out there that personally, I had questions on whether the repassivation potential seen after you get breakdown from the F2129 testing is reflective of the true passivation potential that you've actually seen after fretting wear.

So we'll go Brian -- or Spiro, Brian, and then Cliff.

DR. MEGREMIS: Yeah, there is a big difference between how something repassivates in the repassivation kinetics at different potentials. So, in other words, if you're at a nice potential where you have a nice tenacious oxide and you scratch it, it will easily -- you know, again, this gets into what type of alloy, but you take cobalt-chrome or titanium, and if you're right around 100 mV, and you could scratch it all day long and it will keep repassivating. That's a different subject between your repassivation potential as measured in F2129.

The kinetics of the oxide reformation, that gets more into kind of the fretting corrosion test, and that gets into another discussion of whether or not doing a bunch of loading of a sample and then doing F2129 is really telling you much about fretting. So those are kind of separate issues.

So I guess I'll just say that doesn't necessarily answer the question of whether or not I think the repassivation potential is a valuable number. So I'll say that really quick. I mean, in the absence of worrying

about regulatory, putting a number out there and worrying about someone rejecting or accepting your sample, it's I think a valuable number to have, although, just like Valeska says, sometimes you might have to run the test a couple of different times to get -- for certain alloys, if you get to a certain potential and then you have to grow a pit, you basically -- and then have to come back down, the value of that sample is debatable.

DR. CHOULES: So I agree with the comment that with fretting, fatigue, or in corrosion, when you have the issue that the protection potential is important, but I think that the tests that we do, which, in those cases, are overlap fatigue testing, those tests typically last a month to eight months even, and I think by assessing it that way, that provides adequate confidence that you're not going to have that issue and that your protection potential is sufficient to view those samples afterwards and look at them and say yes, we don't see any fretting corrosion.

DR. WARNER: So just to add to a couple comments already made in this area.

So, certainly, it's been extremely well documented in literature that the repassivation potential is a function of pit volume. I mean, that's well known. And to one extreme of that, you go to a somewhat of stillborn method coming out of G01, which is trying to use what's called the method for stents where Tsugikawa Hisamatsu electrochemical method, where they grow massive pits in materials. And these are folks that are trying to study

nuclear reactor -- you know, waste containment systems for nuclear materials.

So that's one end of it, and they view that as a material parameter that they can hang their hat on for thousands, if not millions, of years. And so the question then comes in the debate, as I've been reading through on the emails is the end of it all, okay, so is that perspective valid here in what we're trying to do with medical devices, and some people are saying, well, probably not, what we're more concerned about in repassivation is if we form a small pit, will that spontaneously repassivate?

Well, the person that kind of -- and I'm not familiar with some references, Jack, that you made, but Barry Syrett at SRI certainly looked at that and what he studied and what he did with his pitting -- I forget, PPR technique, which, if you think 746 is bad, this is really onerous. But it's a whole study, series of studies, that lets you get at some of the repassivation kinetics in a material for small pits.

And, you know, so all of these things point to the fact that yeah, we created ASTM F2129, and yes, it's an international standards committee, so, you know, there are certain aspects about working within standards that have an impact on what comes out of it. But it was the best shot for a number of people involved to try and come up with something that we could start generating some data in a consistent manner between various parties.

Certainly, as we revisit these parameters, and E_p is certainly one of them, it may be one of those that we have to say, you know what, you can't just lump everything on one test method and get what you need; you're going to have to some more work in certain cases. And we might need to dust off Barry Syrett's work and say is there another approach than 746 to kind of get at what he was trying to get at. And so, you know, I think when we look at these things, we're going to have to take that in mind.

DR. SCHROEDER: I had a comment going back to Erica's and then Spiro touched on the repassivation in F2129 versus -- or what it means for fretting. And I don't see that those are too related, that you know, in the pitting environment, you got a micro environment, you got an acidic pit, the volume is going to affect your ability to repassivate.

And in fretting, you're not controlling the potential; you're going to passivate immediately. You're probably going to drop potential and then rise back up. But I think that those are very different and don't really reflect on each other.

DR. LEMONS: Returning to the details. Again, Jack Lemons.

When you have repassivation, it means that you removed, initially by some phenomena, the passive layer; that's normally an oxide or some type of a compound. Those debris that are generated during that process are very different than one another, and if you then develop, say, a micro or nano dimension particulate, in some systems that's a significantly

cold work particulate.

In some systems, that the kinetics leads to the reformation of an oxide immediately, but in order to find and form the secondary compounds that influence the continuation of corrosion, it normally requires an ionic specie that's going to complex with those things in the environment like chlorine or the other compounds that will form a complex to change local pH.

So the point I hope to make, by carrying us into the science, is many years ago, in the references that I referred to, that was the issue, and it was primarily with articulation. But I think those that are quite valuable in terms of thinking about any test methodology because it depends upon the various specifics of the particular biomaterial that one is considering for passivation/repassivation, and then secondarily, what is the reaction of that debris product that's generated locally that may influence the outcome.

Now, this gets a lot more complicated than running a simple in vitro test, and I think, once again, to simulate that would be the only way you'd get that information, I think, is to look at in vivo outcome.

DR. TAKAI: All right, so to sort of transition to what we're going to talk about after lunch, which is how we might want to change the F2129 testing, we asked folks what other testing concerns folks had regarding corrosion testing, and basically we asked if you had concerns about other limitations on the current corrosion test methods.

Most people said yes, there were concerns, and even though we asked the question more generally, people were concentrating on F2129 testing probably because of the way the homework was. So some of the comments that we saw were that it's a fine screening tool, but because of the lack of in vivo correlations, that's kind of problematic; the lack of calibration criteria, so basically the variability across your test runs might be fairly large and it's difficult to discern these variations across runs to testing across different devices.

Other concern that commonly came up was the effect of the solution. I think Jack's mentioned this a number of times as well. For instance, things like the lack of pH fluctuations that would happen in vivo; you don't really have that in a buffered solution and in vitro test setup, the composition, although most people use PBS, you know, whether it is or isn't the best idea. De-aeration is also commonly used with F2129 tests, but in vivo, you have oxygen in your blood, so you know the effects of that.

So maybe we could have folks start off discussing some of the corrosion testing concerns, and keep in mind that this afternoon after lunch, we'll be talking about potential changes to test methods.

Sascha.

MR. KAMMER: Sascha Kammer, Pfm Medical.

For example, if I have two nitinol materials, one material, different test, I have a high E_b of, let's say, 1000 mV and other material has a

low E_b of, let's say, 200 mV, so then I would say, according to -- I would choose the material with the 1000 mV. It's safer, it's better.

But then I do a nickel leaching test and then I see, during the nickel leaching test, the material with the high E_b has a higher leaching than the material for low E_b. What shall I do now?

DR. TAKAI: So I'm not sure if you wanted folks to discuss that or if that was kind of a rhetorical question, but I would assume that, you know, you would look at the risk/benefit of the various characteristics and determine your materials from that.

Jack, did you have a comment?

DR. LEMONS: No, I mistakenly --

DR. TAKAI: Okay.

MR. MARTINEZ: I guess my question is a hypothetical question because it can give you a hypothetical answer. Or is it something you've experienced with an actual material?

MR. KAMMER: It's test results, yes.

DR. EISELSTEIN: Actually, my experience has sort of been different from that, in that what I have seen is that with my electropolished, I actually had a lower nickel release rate than I did on the thermal oxide nitinol that had a much lower E_b, and actually, it was such that the E_b-E_r values were much more variable for the electropolished, but the very low E_b values or E_b-E_r values I was measuring on the thermally oxidized material were much

lower, but they were much more tightly controlled. They'd all break down, you know, 300 mV plus or minus 50 or something like that. However, its nickel leaching rate was much higher. So I think it really depends on what type of tests you do and how you treat your -- and how you passivate, how you electropolish.

The other item that you brought up was the de-aeration issue. I think most electrochemists would argue that really, when you're doing a cyclic pulverization test, you have tested, de-aerate, and otherwise you get the confounding factor of dissolved oxygen on the value, so it has to be done that way.

So the way to avoid that, I think, is maybe one that I had suggested a little bit earlier, which is that if you really want to see the effect of oxygen or an oxygenated in vivo environment, pre-expose your sample to an oxygenated environment before you do the test. Just don't take it out of the package and test it. You can actually pre-expose it.

You could potentially do the same thing to address the pH fluctuations, although some of the pH fluctuations could probably, I think, as you pointed out, they can do some severe damage if the pH goes much below about 5.

DR. BERG: Brian Berg. Couple comments.

One is associated with, you know, before you ever take a summary statistic of any test, make sure you look at the entire test curve

because there's a lot of information in there that you're throwing away unnecessarily if you're just taking summary statistics. And you can also misinterpret tests if you're not understanding what the full curve means. So that's the first point.

Second point is there's a huge difference between the use of the test for regulatory submission and process development. That is, make sure that you understand that the test results that you're getting are maybe indicative of something in the development, but you have a clear direction of what's better. Obviously, higher breakdowns and lower nickel leaching, those types of things are things that we want to get to, but in terms of what's acceptable, well, that's in all honesty an impossibility to know that you'll be absolutely safe. So perhaps better is, again, emphasize looking towards known problems that might be associated with the tests.

And right now, I don't see a lot of direct guidance in how to use the F2129 to avoid known problems. All we're, at this stage, saying is use the test to try to make your device better.

DR. TAKAI: That's a good point, and it's difficult because as we've also alluded earlier, we don't know where the clear cutoff is on what's acceptable or what's even an unacceptable value that will be correlated to unacceptable results in vivo.

So before we break for lunch, do people have any last comments?

Oh, I'm sorry, Valeska.

DR. SCHROEDER: I'll make one more comment about testing concerns, and I'm not sure if the intent was details of testing, but this is a little bit more general.

I think a lot of our experience, and that was reflected in the homework, is with a limited number of metals, 316L, the cobalt-chromes, and nitinol. And I think whether or not we directly use predicate devices, that we base a lot of our judgment on whether the test results are good or bad on predicate device experience, and I guess my biggest concern is that if I had a new material, something truly different, would I feel comfortable using this test to say that this was acceptable for a first time use, and I would have some issue with that.

So I have a lot more comfort in using the test to do something similar, you know, use my electropolished nitinol, modify it, improve my manufacturing conditions as opposed to try something really different.

MR. MARTINEZ: I guess I'd like to make a final comment here.

In the past I made comments in regard to how optimistic it was to pretend to do predictions in vivo with the F2129; that's still very true for myself and for the rest of the scientists in the company that deal with corrosion.

But I'd like to underscore a very important point, that this is not a bad test. We use it, we'll continue to use it, and Ken asked before

about what is in it for the FDA in here, and I can tell you that there are a lot of things we can do to maintain the quality of the products.

For example, for compliance testing, every time there is a change in the processing, in the process or a vendor or something, we use that test. So that data we generate internally that we compare to predicate product with field history is extremely valuable to ensure the safety of our devices. This is kind of like the canary in the coal mine.

If you see a change in the process, immediately what you do, as a corrosion scientist, is investigate. You have to do the microscopy work. You have to understand the metallurgical changes, processing of the vendor. So this is a very good way to ensure quality. So, again, the fact that we don't correlate it to in vivo is not that it doesn't mean it doesn't have any value. So that's my point.

DR. TAKAI: Brian, did you want to make -- okay.

Spiro.

DR. MEGREMIS: Yeah. I'll just say, with that in mind, it has also been very important, when we start talking about making changes, F2129, to be careful about that because there's a lot of valuable information that's been gathered over the years, and when we start talking about getting rid of repassivation potential and things like that, we have to be careful about, well, is that going to take away some information, good information, that's been being gathered for a while.

DR. TAKAI: Agreed.

I'll say this again. After lunch, but the intent here isn't to replicate the work of the F2129 group. You know, we're looking more at methods, for example, like the pre- and post-fatigue testing that are outside the scope of F2129. We want to discuss those sort of things after lunch.

So just from a logistical standpoint, because of people up here probably can't be eating, finishing up their food when the next session starts, can folks try to let them get lunch, purchase lunch first, if at all possible?

So one of our speakers for the afternoon session has become ill, so we're going to adjust time a little bit. So if everybody can come back here by a little bit before 1:15, and we'll commence again at 1:15.

Thanks, all.

(Whereupon, at 12:15 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

DR. TAKAI: All right, I hope people had a reasonable lunch, and I hope you had some good sidebar conversations and are ready to continue on with some more.

So the last objective for our corrosion session is to discuss how corrosion should be assessed moving forward. I'll show again some homework results, and then we'll go into discussions.

So the first general area is whether F2129 as an assessment of clinically relevant corrosion is sufficient or not, and when we asked this in the homework, we got roughly half of the folks saying no, it's not sufficient, and the rest of the people saying yes or not sure/maybe. I think part of the confusion with this question also is whether or not we meant F2129 alone versus in combination with other tests. We're hoping that people can think about it in both regards, you know, is F2129 as it is okay and, you know, whether or not you need to have other tests also in addition to F2129.

And when we asked folks if there is a way to modify it, the split was pretty similar as well. About half said yes, there is a way that it could be modified, a quarter said no, and another quarter said, well, maybe/we don't know. But interestingly, really, there is only one response saying that you should just completely replace F2129 with other tests and not do it at all. So overall it seems like folks think that there is value in doing this test, which is also reflective of our discussions this morning.

So when we asked folks if there is a way to modify it, some of the common narrative responses we got was that there is a need to correlate the values to in vivo outcomes and also, you know, while it's a good general indication of corrosion resistance, it's not sufficient alone, and we really need to be adding things like fretting assessments or nickel leach testing.

Another common response we got was the PDP curves should really be assessed more deeply, I think, for example like the Tafel characteristics, the repassivation portion of the curve, active pitting and pitting propagation. So I think, you know, we had a comment earlier this morning, also don't just look at the summary data, you know, actually look at the curves. I think it's reflected here.

So now we would like you to have this discussion about whether ASTM F2129 is a sufficient assessment of clinically relevant corrosion, and if not, how you might modify it and what other assessments might constitute a clinically relevant assessment of corrosion. And if people know of other standards other than F2129, maybe you can incorporate that as well.

Oh, and before we start the discussions, the transcriptionist asked that you really speak into the microphone because the folks in the audience can't really hear well if you're not speaking well into the microphone, and also to remember to say who you are before you speak.

So maybe we could continue with this question about how you

might want to modify F2129 if it's not a sufficient assessment of corrosion.

DR. KRAMER-BROWN: Pamela Kramer-Brown with Abbott.

I think we might be going down a divergent pathway. F2129, as the discussion has really mentioned, is an excellent test to look at some things with regard to an implant. Whether it's fully clinically relevant is in question. However, also as an ASTM committee member for F2129, I can say that a lot of thought went into how to perform the test, to also make it a useable test within a reasonable timeframe for the users.

So any modifications may take it out of that bailiwick, and I would actually suggest looking into what other people have recommended, which is adding in other tests that may have better clinical relevance.

DR. TAKAI: Sure. So I guess the question here then is basically the question of what is a clinically relevant assessment of corrosion? So what other tests do people think should be considered to assess corrosion?

I know some people had said in the homework that other assessments included things like open circuit potential measurements and so forth, so if people could elaborate on that. Okay, so maybe people are a little afraid to say things, also, because you're worried that, well, you know, if we say there are these other tests, that FDA going to start requiring more tests, but that's not necessarily the case here. We just want to try to get a better idea of what would give us a more complete picture of the corrosion potential or risks associated with devices. And these are just things to

consider, not necessarily you must do them all the time.

Larry.

DR. EISELSTEIN: Well, I guess, just to get the ball rolling, I think the major concern about F2129 is really the lack of correlation with clinical results. The clinical results seem to indicate to me that there isn't much of a problem with corrosion in general.

So having said that, you know, how could F2129 be improved? I think I had mentioned before that, and I think your comment just previously, would maybe argue against this, but one way it could be improved -- and maybe you don't have to change the standard, but you could say that, you know, it's likely that you'll get more realistic clinical values of E_b and E_r if you pre-expose some samples. Now, you might not want to make that mandatory, but you could put it in as an alternate way of testing samples that have been pre-exposed to aerated solutions. So that might be one way.

The other question is, well, what other tests might be clinically relevant? And that question can't be addressed in the absence of understanding what the end form of the device actually is. If it's a stent that's likely to be overlapped or it could be overlapped at some point in the future, you would then think that perhaps doing, you know, corrosion fatigue testing at the very least, which I think is potentially required anyway, would be of interest.

And other than that, the other factor that may be relevant

would be the rate of nickel release, which to my way of thinking is potentially a way of measuring the corrosion resistance. Actually, it may be a little bit more sensitive than even is possible with the ASTM F2129 test because you can measure some very, very low nickel dissolution rates with ICP mass spec, and those equivalent rates are usually significantly below anything you could probably get with your potentiostat.

So that begs the question again, though, are even the nickel release rates that you're getting from your device, are they clinically relevant? And I don't know. I think we'll be talking about that sometime later. But obviously nickel release rates or other metal ion release rates is another, I think, very useful parameter to evaluate the corrosion performance of your device.

DR. TAKAI: So I think, also, a question, a follow-on to that is so we've been concentrating a lot on F2129, but there are other corrosion methods out there. Do people generally think that F2129 is probably the best one out there that we're using to date in terms of pitting and crevice corrosion, or do people think that there are other methodologies that are in standards?

Shari.

DR. ROSENBLOOM: Shari Rosenbloom, Corrosion Testing Labs.

I guess I heard the question two ways, actually. I first heard it as what are the -- what's the possible suite of tests we might want to perform

to assess corrosion? But then when you restated it a minute ago, you asked whether this was the best to assess pitting, and that's only one particular form of corrosion.

I guess when I look at what's available to us -- and what Pamela said is really right about being careful about selecting tests that can be done in a reasonable time frame without putting device manufacturers under, you know, too much financial or time stress. So F2129 does a pretty good job of assessing, and certainly it's an aggressive test. And if you want to look at a really worst case situation and get a sense of what's going on with the device in terms of pitting specifically, I think that's a pretty good test. Whether that correlates with in vivo is a whole other issue.

In terms of the whole suite of tests, though, I would say that that's really the first test that we look at to run when somebody comes to us, as a test lab, and says what do you think we should do? We always say we'll do F2129 first; it's fast, it's aggressive, and if you do well in that, we can move on.

And then beyond that, we look at, again, where is this device going to go and how is it potentially going to be used, how do we anticipate it's going to be used, and then how might it be used that we might not anticipate because things do get used in other ways. And at that point we look at the galvanic test. Right now it's available as ASTM G71 as a standard, but right now in ASTM committee, there's a new galvanic standard

specifically for medical devices that's going through the process of becoming a standard. And so hopefully, sometime in the near future, we will have a medical -- just like F2129 is to medical devices, a standard for galvanic. And I think that that's an important test.

You mention up there the ISO 16429, that's a long-term open circuit potential test. It's a very broad kind of a guideline, and you can add the nickel leaching on to it. You know, we do look at that test, you know, and we could maybe talk about developing a standard for doing that kind of testing at ASTM or doing -- including the nickel leaching.

So to me, that's kind of the basic test and then, of course, the fatigue and fretting tests possibly followed by F2129. And when we do that, we've kind of incorporated some of what Larry's been talking about, about pre-exposure and looking for longer-term behavior.

DR. TAKAI: Brian.

DR. CHOULES: The one test that I was thinking about is it may be perfectly appropriate for implants that are not implanted for 10 years. A shorter duration may just be a simple immersion test, and you may learn more from that, especially when you start considering coverings that the stent may or device may have. So just an immersion test is appropriate, can be appropriate for shorter durations.

DR. TAKAI: Can I ask, when you say immersion tests, would you be assessing pitting or evidence of corrosion at the end of that, or would you

be monitoring open circuit potential in the meantime or nickel release, or what else would you be --

DR. CHOULES: I would just simply do visual SEM observations at different time points and not monitor the open circuit potential.

DR. TAKAI: Jack and then Larry.

DR. LEMONS: I would make the point that I take the opposite position with regard to F2129. Most of the stents in clinical use today are performing as intended. Most of the stents in clinical use today have been subjected to this test, so we might take the position that it's working quite well.

Now, let's go to the other side and say, well, there are circumstances there that may be of concern, but those are really addressing different questions. So I think we have to be very specific to the question that we need to answer if we're going to develop a new standard, and as we've heard from several, that's going on.

There is also intended, with AMA, ASTM, whatever and whatever, to have a division of effort where we're not duplicating the same thing in several theaters. So I think there needs to be a decision where these specific standards need to evolve and who is going to do them with adequate participation. And ASTM or AMA involvement in ISO, you know, I think is the pathway, but it has to be decided because there's no reason to take a standard and then duplicate it in another theater.

DR. TAKAI: Completely agreed. And I want to reiterate the point that -- and remind myself of the point that I made before lunch, which is we're not trying to redo the F2129 test. I think a lot of the things and practical application of the F2129 are not actually spelled out in that standard, like, for instance, what do you do if you're going to do a post-fatigue test? How do you deal with your device? If you have a covering on your device, what do you do about that? Do you scratch it or do you leave it alone or what?

So I was hoping that we can have some discussion on those sort of more practical application issues for F2129 as well.

But Larry.

MR. KAY: Larry Kay with Fort Wayne Metals.

Just from the environmental side of the test, to me it seems like there's some discrepancies, some areas that need to be addressed. We talked earlier about the aeration issue, and Spiro mentioned it this morning, too. But the environment that we see in terms of the proteins and the other cells that are involved, you know, we're starting to do some fatigue testing by applying proteins and other cells to the surfaces, and we're seeing very different results in fatigue testing. And so I think we need to consider those kinds of changes.

And, again, there are still discrepancies. You guys have talked about the in vivo and in vitro, and even from a raw materials perspective, you

showed the data earlier this morning about the cobalt-chrome materials for which there was a fair number of breakdowns measured. We haven't seen that at all in materials, so I don't know what you guys are doing to this wire we're giving you, but there's a problem with it.

(Laughter.)

DR. TAKAI: Cliff.

DR. WARNER: Cliff Warner of W. L. Gore. So I think, in terms of your broader question about what else are you doing and is ASTM F2129 sufficient by itself, if you go back to, you know, some of the -- when Rick Corbett came up with his 600 mV thing, what's not been said here at all and hasn't been repeated is the second half of his statement around that value, and that was all around lacking any other information. It was based on if you were completely lacking any other data. This is something he felt you could hang your hat on. Believe me, I pushed him on that, to understand really where he was coming from.

And I think some of these values are being taken with a very narrow view with just one test and, you know, my personal point of view is I don't think just one simple test can always answer all your questions. These are complicated devices, there are many things going on, and we have to think very carefully about all the different issues in that device and what we need to test for.

The other piece that we haven't talked about today is certainly,

you know, as Brian said, we can do immersion tests, but you can also use animal data. A lot of these devices have to go through various series of testing, and they go into animals and you can get them back out sometimes. Not always, but you can. And I think you can use other pieces of information to build your understanding of how your device is actually performing instead of relying on just a singular value coming out of one in vitro test, and I think it's an important perspective not to lose. So that suffices.

DR. TAKAI: Okay, Valeska and then Brian.

DR. SCHROEDER: I wanted to touch on, as far as other testing that could be done, something that's been brought up, that idea of what's happening over time, and I think that really speaks to a number of the tests that you could do to follow up.

So is your surface becoming more protective or less protective over time? And I think open circuit is a measure of that, I think nickel immersion is a measure of that, and I think doing F2129 at the end of some period of time is also. So there are three ways to measure are you becoming more protective or less protective over time? And I don't think you have to all three of those, but I think one of those can be helpful, especially if you're in a borderline condition in an as-manufactured state.

DR. BERG: Brian Berg.

I think I just want to go back to a point Valeska made earlier, that you have to be really careful about is this test being used for one of the

three alloy systems, or do you kind of make the decision of a new material? Because given the level of evidence that we've seen today, if the device is of those three materials used in pretty much the same cardiovascular conditions that it's being used in today without any significant galvanic situations, I'd argue that you almost don't need to do any testing but F2129, just because we know this material behaves pretty well. And we know that this test is not perfect. I mean, there may be some instances where it's not capturing things, but this test doesn't address those conditions.

So for new alloys, there's a whole range of tests, and I don't think anybody here would say F2129 would be sufficient. And so once you get to that, then you need to start addressing animal testing, long-term testing, a huge variety. So I think it's very important to recognize the difference between new alloy development and these canonical alloys.

DR. TAKAI: Shari and then Gonzalo.

DR. ROSENBLOOM: Shari Rosenbloom.

Two quick things. One, Larry, to just get back to your point about the cobalt-chromium, I agree; I have not seen cobalt-chromium break down. I suspect, as I said earlier, that the values that were reported were actually that change. It was a misinterpretation of the data and that they probably weren't breakdown.

The other thing, Erica, to answer your question about what do we do with F2129 to look at coatings and what should we do -- I forget,

somebody asked that, what should we do about coatings? As a test lab that has no clinical data to look at and all we have are these in vitro tests, we like to look at the worst case, and we like to try to understand what the worst case might be.

So, ideally, when it comes to a coated sample, we might ask our client to consider doing the testing, F2129, on a bare device just to see what the material, itself, the underlying material will do. We might do it with a fully intact coating or at least what they think is a fully intact coating to understand whether or not it is and whether or not it's really insulating. And then we might scratch the coating, and that creates a crevice and that creates a really worst-case situation.

So we might want to look at all of those things if we really, you know, don't have any other data to go on. And, of course, we're always asking, where's the device going to be used and what are the possibilities for any of these things to happen through fretting or contact with something else or delivery, what might happen to that coating?

DR. TAKAI: Gonzalo.

MR. MARTINEZ: Gonzalo from Medtronic, Gonzalo Martinez.

We actually have done all sorts of tests. In fact, before F2129 was called 21, we were doing cyclic polarization tests, which is basically the same. The one thing that we saw is that every time we try to use different solutions, particularly adding protein or any, you know, bovine plasma and all

sorts of things, the return on the investment to try to predict in vivo situations is very low.

In fact, contradictory in this, publications, Stan Brown, Kathy Merritt themselves published contradictory reports in the literature. Sometimes you'll see an increase in corrosion rates; sometimes you'll see a decrease in corrosion rates. So I don't believe you're really going to gain much but complicate the analyses more than where we are right now.

I still maintain, our company maintains, that the best use of this standard is for screening quality assurance in which we compare to a predicate product with good performance.

Now, suggestion for improvement, perhaps do something that you should be doing already is a good microscopy analysis. Remember, there are two phases of corrosion here. One is the signals that you get from your potentiostat which, by the way, could be confounded with artifacts. And the other one is the manifestation of those signals into a physical transformation of your alloy or your material. So at least, to look at those samples with optical microscopy at the minimum and then take it on from there because that's one thing we haven't talked much about.

DR. TAKAI: Larry.

DR. EISELSTEIN: Larry Eiselstein from Exponent.

A couple of comments. I think Brian Berg had pointed out that, what do you do with F2129 with, say, like new alloys that haven't been

developed? I'd just like to point out that, you know, surface modifications and surface treatments in many cases are almost like a new alloy. I've tested materials that have been through surface conditions, and I can say, without a doubt, F2129 got the manufacturer to move in another direction in many cases because it was clearly indicative that that potential improvement was not going to help. So I guess there are two points there.

The other one is that, again, following up on Gonzalo's point, which is that I do believe F2129 is quite helpful with regards to quality assurance, making sure that something hasn't gone awry with the manufacturing techniques. And then it's also very important with helping to screen and select alternate materials and processes.

The sticking point is what's left in the middle here, which is from a regulatory point of view, what do we do, what do we have, should there be something there? And I think we've talked around that, I think you'd like us all to say, well, it should be this, and I think that the consensus is that it's very difficult to say it should be this based on we aren't really sure whether or not this test has any clinical relevance.

DR. TAKAI: Gonzalo.

(No response.)

DR. TAKAI: Okay. So to follow up on that, I think, because everybody's really uncomfortable with stating a number, you know, maybe we could say a range below which practically, when you guys are in your R&D

phase even, what is the range of values below which you say we're not going to use this material anymore or you say, well, you know, this is a gray zone so we need to do other assessments. Can people state some numbers?

Pamela.

DR. KRAMER-BROWN: Actually, I would take the opposite approach. I wouldn't state a number. I don't think that you can put a line in the sand and say that something is absolutely bad until you test it in other ways, especially during the research phase of a project. Having animal data is exceptionally important, as was pointed out, and doing other tests as well. So it actually wouldn't stop a project just because of the one value.

DR. TAKAI: Sure. But if folks are saying that this is a good screening test, to me that means that you do the test and depending on what the numbers are, you decide to do other tests. So I'm not even sure what those numbers are that people are using, so I was hoping people could speak on that a little bit.

DR. KRAMER-BROWN: So just let me make one comment in that I have seen a product which was brought in from the market and tested in-house and it had a breakdown value of 0 mV. And you showed data here which showed some quite low values. We don't have an internal number, I'll tell you that, because it's an "it depends" sort of scenario. I know you're trying to get us to draw a line, and I know I can't.

DR. TAKAI: Larry.

DR. EISELSTEIN: Yeah, I'm not sure that -- facetiously, I think there is, you know, numbers in which -- I think we talked about that at lunch -- would, you know, obviously cause concern. So, for instance, if you have a breakdown potential that is -- you know is going to be lower than what the in vivo potentials are, so for instance, you drop it in a beaker of PBS that's aerated and you don't want your sample to be biodegradable and you start seeing it bubble and dissolve before your eyes --

(Laughter.)

DR. EISELSTEIN: -- you would know that that's probably not going to be acceptable. So now the real question is, well, where do you draw that line? So, again, this points to the lack of good long-term in vivo measurements or even animal measurements.

But typically what I have seen is that, you know, probably about the maximum credible long-term E_r value you can get on devices that have been measured, you know, is probably no higher than 200 mV. And it's probably not much -- it might not be much higher than zero. But, you know, somewhere between 0 and 200, I mean, I would really start questioning the -- you know, particularly if I had -- you know, again, I'm not a manufacturer, so I sometimes don't know what their constraints are, but certainly if I were designing something that had enough lead time, I would reconsider basically redesigning the system in order to get that breakdown potential somewhere, you know, above 200 mV and above 200 mV on a consistent factor.

But it's really the E_b-E_r. So, for instance, if you know that, for instance, your long-term in vivo rest potential is going to be -200 and your device has a breakdown potential that's zero, then that ought to be fine.

So, again, I think it should be predicated on the basis of some indication of what the long-term E_r is in an aerated environment and that the breakdown potential should be significantly above that so you can say with, you know, 95%, 99% certainty, that with high confidence that you'll be above that level.

DR. TAKAI: So I think part of the reason why I keep on asking this question is because we've danced around this question of, well, you know, so F2129 is not the be all and end all, you know; it's just one piece of the puzzle, and we need to think about other assessments also. But we don't really know when we should be looking at these various other assessments, and I'm guessing that functionally what people are doing is when your E_b and E_b-E_r values are of a certain range, you might do more of these other tests.

So we don't need to discuss it right here. After we talk about the other tests in the other sessions and the summary session, maybe we could revisit this question again. So I'm going to move on now to the potential modifications to testing methodologies. So, again, we're not going to be talking about necessarily changing the F2129 testing itself, but more of the applications of how you would practically do things.

So, you know, we asked some questions about best practices

and whether or not folks use a control. And roughly, a little bit more than a quarter or about a quarter said yes, you know, we use a control. Another much larger chunk said if appropriate, maybe sometimes. And a smaller fraction said no.

When we asked about the sample sizes used, the median values here are shown. They range from about 5 to 10, and I think the differences here are reflective on the fact that nitinol has a larger variability than cobalt-chrome, typically.

So revisiting this issue of covered or coated devices, we asked folks if you intentionally damage the coating or covering, and 75% of you said yes, we do some sort of damage. And the folks that said that they do, it was mainly due to simulated use testing, and this could be either acute, so just deployment, or after fatigue. There was one response where they said that they intentionally scratch the covering to create damage.

And when we look at the different device alloys for the covered and coated, we noted that all the no's came from covered or coated cobalt-chrome devices, and all the folks that made covered or coated stainless steel devices said okay, you know, we always induce some sort of damage.

So surrounding these modification issues, we'd like you to discuss possible modifications in how you apply the F2129 test. Maybe we could start off by discussing the problems or concerns surrounding using post-fatigue samples for the F2129 testing.

Okay, Shari.

DR. ROSENBLOOM: Shari Rosenbloom.

Well, there are a few. There are few issues that I'll speak about, and I know other people will bring up others with regards to the post-fatigue, the first being that there is no standard right now that tells us how to do that. So I don't know that there's consistency out there in what people are doing, and it has been discussed at ASTM, and we haven't yet settled on whether we should write a standard and what that standard would be like if we wrote it. So that's one.

Another one is, practically speaking, how do you do this test? So you've got, you know, for your F2129, it's a deaerated environment, and you take the samples that are provided and you prepare them and you put them in -- and you test them.

But for the post-fatigue, they've been exposed in a solution, and typically the way that the test is done, you're not going to then go immediately and run your F2129. It's going to be removed from the mock vessel or whatever, you know, and it's going to possibly even transfer solutions, you know, into the F2129 test vessel, and the fatigue may have been done aerated and now you're going to test de-aerate it and you're going to have all of the potential -- I don't want to call them problems, but variables that get introduced by all of this handling and by the differences in how people might do that. So I think that that's something that needs to be

discussed and hopefully settled on in terms of how -- what's best practices for doing that.

DR. TAKAI: I guess part of the question surrounding this post-fatigue issue is, so we know from earlier discussions, and Larry has brought this up a couple of times, that if you have your metallic device sitting in even just a vat of solution for a period of time, your E_b and your E_r are likely going to shift. Now, that's one consideration.

And then the other consideration is, well, the post-fatigue means the tests presumably will induce some sort of damage if there's fretting expected, but that sort of behavior would be captured as well.

So the question here is if we ignore that portion, would we be missing a big chunk of information if we just took the device and had it sitting in a vat as opposed to doing it truly post-fatigue, you know, will we be losing a lot of information?

Larry.

DR. EISELSTEIN: I'll try to address that and one of Shari's concerns as well. We've done some post-fatigue, tested ASTM F2129 tests and actually generally see, you know, the same or maybe better properties with regards to E_b-E_r.

And, again, I think the issue you brought up which is, you know, there isn't any standard. But I think you're absolutely right, you know, you don't want to let your specimen dry out and you probably don't want to delay

much between the end of that test and -- I mean, we could go in and try to provide guidelines for that.

But the question is, the question you brought up is, well, what difference could there be between, say, just pre-exposing it in a solution versus actually doing a test? And there is potentially one real big difference, which is if you're doing your fatigue test, for instance, with overlap stents, that might be different materials even. Then you could have some substantial differences as a result of that, particularly if there is indication of fretting.

Now, I've actually done F2129 tests on samples that when we looked at it after the test, that had been fatigued tested, have indications that there was some, if not just as much, fretting as we saw in some of the pictures up there, but it did not seem to have much of an effect on the E_b-E_r values.

So, you know, theoretically, there could be some big differences, but in actual fact, I think that, you know, just sort of soaking them for a time period is perhaps good enough. But, again, that's just my limited perspective from my limited testing.

DR. TAKAI: Cliff and then Ken.

DR. WARNER: Cliff Warner with Gore.

I think there is -- some of the discussion that's been around on this subject of using post-fatigue testing with F2129 gets down to questions

about how do you actually handle the samples? I mean, there are some real technical issues here. If you have to have electrical connections to the device throughout the whole fatigue cycle, so you keep it wet and never dry it out because otherwise you have a real practical problem of how do you attach this thing without causing other issues in your test method?

So there are some technical hurdles to actually implementing this that really we haven't had the time, I think, in the ASTM meetings to really kind of get to brass tacks, is this feasible or not? And that discussion needs to happen.

I also question, given -- you know, we also have tried to do this test method and look at it and we see similar things. We see values getting better. What's the value of going through all those technical hurdles versus simply going in and doing a very thorough and detailed visual analysis, you know, as we talked about before, as Brian suggested. That has a lot of value, and yeah, we should be looking at our devices post-fatigue and seeing what we see. That is a potential alternative that potentially is much less complicated and gives you very direct results.

DR. TAKAI: Ken.

DR. CAVANAUGH: Ken Cavanaugh.

So I was debating about putting my card down because I think some of the things I was going to say were said, but I'll talk anyway. I think the question about testing post-fatigue is an important one, and I think folks

have talked about some of the considerations that go into doing the tests and I guess interpreting the results. Looking at the homework assignment that was given, perhaps maybe a subpart of the question about how to do F2129 testing would also be, well, what role does post-fatigue testing play for that particular test, not fretting, which makes sense. Post-fatigue may be in a different way than this does.

But thinking about what do you learn from that test post-fatigue versus doing it pre-fatigue. Are there advantages and disadvantages to doing it post-fatigue and thinking about how you put the results of that test in context with pre-fatigue testing? Can post-fatigue testing stand by itself, can pre-fatigue testing stand by itself, just thinking about it from that standpoint.

I guess the question -- really, one of the questions I would really be asking is, for those folks who do post-fatigue testing, do you do that because it adds value to your assessment of the suitability of your designing your materials, or did you do it because your perception was that a regulatory authority was going to make you do it?

And I'm just trying to think about, you know, what you get out of these particular tests. Again, thinking about what's in it for Ken. What do you get out of these tests and thinking about the total package of data you would collect. You know, I understand we have limited time with this workshop, but it may be helpful to get some of those ideas and perspectives

out there and open them. We're thinking about how to optimize, I guess, testing strategies for corrosion.

DR. TAKAI: So maybe if we can zone in to Ken's granular question of, you know, do you think it's worthwhile to do the F2129 test post-fatigue, maybe people could share a little bit more of their thoughts on that.

DR. KRAMER-BROWN: I mean, not just from a device manufacturer perspective, but from a scientific perspective, I would agree with the statements that have been made about the visual inspection and really needing to understand and see what's happening with your device, especially in an overlapped configuration. To me, the F2129 test is not going to add anything to that. That's my personal opinion.

DR. TAKAI: Before I move on to a different question, did anybody else have -- okay.

DR. EISELSTEIN: I would also agree with that, in that if you manage to make it through, you know, fatigue testing in an overlapped condition for, you know, six months of testing, as well as having done, you know, F2129 tests and you didn't get some squirrelly results early on, you know, you're probably going to be good.

I think, again, one of the things I look at is, I look at -- but again, now, one of the other things you might want to consider, though, is that, you know, you spend six months testing these things and they're still available to do some work on it, you know. It's a little incremental cost to do the extra

test, but that might be one.

The reason that you might want to do that is that -- but I think you could do this with an immersion test as well -- is that I think that E_b-E_r sort of represents the safety factor over, you know, how much margin do you have on your system. Again, it's like doing a fatigue test. Well, I tested it under physiological conditions and it didn't break. Well, how robust is that, you know, unless you stress it higher and higher and higher until you get a failure? You don't really know what your safety factor is.

And so by allowing -- and so one of the arguments about why E_b-E_r in a normal ASTM F2129 test might not be reasonable is that people argue, well, that E_r value isn't necessarily what's reflective of long-term in vivo exposure.

And so, in effect, I look at the -- it's just sort of a little bit extra you can do at the end of, you know, your fatigue test, you can actually measure, you know, E_b and E_r on those. They've been exposed for God knows how long, and now you can say, well, I can compare that to what I had before and it hasn't changed very much, or E_r has maybe increased, E_b maybe has increased a little bit too, but, you know, nothing has gone wrong. And it allows you to get away from this issue of E_b-E_r sort of being a margin of safety against pitting, but you don't really know exactly what the in vivo E_r value is.

DR. TAKAI: Okay. Emily and then James.

DR. McLUCAS: Emily McLucas.

I think both things should be done together because a visual inspection, you may get some -- you may detect some issues. But you can't necessarily correlate that with an in vivo response, either. So, therefore, if you do an ASTM F2129 test and do a visual inspection together, at least you can kind of see how, you know, your visual inspection results correlate with corrosion resistance.

MR. SCUTTI: Hi. James Scutti, Atrium Medical.

To answer Ken's question there, I think focusing on a worst case situation is effective, and certainly a worst case doing F2129 post-fatigue could give a lot of good information that once that's shown to be safe, then there are some good conclusions that can be made based on the durability, corrosion durability, of that device.

DR. TAKAI: Gonzalo and then Spiro.

MR. MARTINEZ: My suspicion is, to answer Ken's question, that people do it because the FDA is asking them to do it. Because when you look at this thing from a corrosion scientist perspective, I think you can add value. I mean, I can run an ASTM 746, too. I can run a whole variety of tests. But I can tell you I can run EPM spectroscopy and follow that over time, which I think is maybe better.

But the bottom line here is fundamentally what you gain versus what you'll spend. I think we need to challenge that. What is the value? I mean yes, you've got that information, then what are you going to do with it?

What sort of decisions are you going to make? I mean, is that going to change the fact? And what alloy system are you working with?

I mean, I can tell you, in MP35N, right, I can scratch MP35N -- Jeremy Gilbert and I, we started years ago and did some wonderful studies on MP35N dynamic corrosion testing. And he did wonderful work on repassivation.

I already know that if you scratch the surface of MP35N and I run an ASTM F2129, you will probably end up with a little lower breakdown potential, but the material still works well in vivo. So what are you gaining? So I think that has to be challenged.

I think that the bottom line, everybody has to do good microscopy work, and we can mine much more useful information from that. So I understand the benefit of doing it, but still I can tell you a whole long list of other tests that would be equally as useful. I think the law of diminishing return applies here.

But my recommendation is basically leave it as an optional test. I don't see a value for all systems; maybe for some systems do, but not all of them.

DR. MEGREMIS: Spiro Megremis, ADA.

Yeah, I probably could have put my sign down because that's what I was -- I guess it gets to the point of what you're trying to get with that test, and if you're really trying to get fretting corrosion data, that test doesn't

really give you fretting corrosion data. It gives you an indication if your oxide has been permanently damaged or altered during that cyclic fatigue cycle, which you could probably see just by visual inspection, because otherwise, if you -- and it doesn't need to be in aerated solution. If you put it on in any type of solution where you can get oxygen that will react with your surface, it will repassivate.

And so yeah, I think it has limited value electrochemically as a test. I mean, it might have some type of value telling you, after you do a certain amount of cycles if -- then you can put it back in solution and do an electrochemical test on it, how it looks. But unless you do some permanent damage to it, I would think it wouldn't look much different than what it looks like before. And that's coming from somebody that doesn't do stent testing, normally.

DR. TAKAI: Sepehr.

DR. FARIABI: Sepehr Fariabi.

What you're really missing is the correlation between F2129 versus in vivo. I think one could actually develop a test method of getting E_b of 100, 200, 300, whatever your range would be, and implant those into the animals and see what correlation we can find. If there is a real correlation, we should be able to see that with the tissue reactions as well as the F2129 testing.

And the other thing or the other comment that I had, if the

guidance does not require you to do corrosion testing for the -- corrosion, it requires you to do the testing after 40 cycles -- or after fatigue/post-fatigue. What I don't recall is whether that is required to test at time zero as well. Maybe it's missing or I'm missing that, but I didn't see that.

DR. TAKAI: No, I'm glad you brought that up. So my question, my follow-up question, was going to be if you were going to do the F2129 test once, is it more valuable to do it on an as-manufactured sample or is it better to do it just on that post-fatigue sample?

DR. FARIABI: I think you should do it on both.

DR. WOODS: Terry Woods, FDA.

And while you're thinking about that, I guess the other question I'd like to ask the people that do these fatigue tests and then try to do the post-fatigue at 2129 is something Cliff brought up.

It seems like a very difficult thing to do. You don't have very many samples that you can do this to, and realistically are you able to do F2129 post-fatigue on enough samples, first of all, to get a few samples' worth of data, and then what does the data mean? Because there are so many variables about how you get it out of the tube, what you do to it between then and when you test it. Can you do it after you've done some kind of SEM examination? I'm just curious what the companies think about this, you know, is it a waste of time to do F2129 after fatigue testing?

DR. TAKAI: Gary, did you want to say something? Okay.

DR. CHOULES: Brian Choules.

We don't know what the results mean at time zero much less after fatigue.

(Laughter.)

DR. CHOULES: So, you know, what happens if you get a decrease in your breakdown potential or EB-E_r? But most of the data indicate that it gets better, so it doesn't seem like you would want to do it afterward as your only test since things are getting better.

DR. TAKAI: I guess, practically speaking, we've seen it go both ways, so it's hard to say if it's always better or worse, although I think, as you mentioned, a lot of cases, the shift is upward, so both E_b and E_b-E_r go up.

Sepehr, did you have another comment or did you just -- okay.

Okay, so what I'm hearing here is that there is, perhaps, not a lot of value added to doing the post-fatigue F2129 perhaps, especially given that we don't really know, you know, if the values go down, you know, what does that mean? There are lots of practical challenges associated that I think many of you have voiced and Terry has also asked about in doing the test post-fatigue.

But are there any last comments before I ask a separate question? Sorry, Valeska.

DR. SCHROEDER: I'm not a big proponent of it; I'll start by saying that. But one thing that was mentioned before was coating and

damaging your coating in a clinically relevant way. And that's an area where maybe the right way is not overlap for 400 million cycles, but maybe you do a higher strain for 5 million cycles or you somehow use overlap fatigue to create a clinically relevant damage to the coating, so that's an area that I see some value in.

DR. TAKAI: Emily.

DR. McLUCAS: Emily McLucas.

The purpose of the post-fatigue test, though, is to evaluate the corrosion resistance of damage that could have been induced during fatigue, so it's sort of a separate question to do pre-fatigue because, for a good surface, the corrosion resistance will decrease after fatigue because of the nickel leaching during the testing. But for a device that isn't performing as well, if there is damage induced during fatigue, you need to evaluate that after fatigue as well.

DR. TAKAI: So I guess my leading -- so that was a perfect setup for my next question. So if you have, for example, a coating or a covering or even if you don't, you know, does it make sense to induce damage to your device? Is that really the same as actually using a device that was damaged through fatigue? So, for example, if you took some sandpaper to your device or you snipped it, is it really the same?

MR. MARTINEZ: I can answer that, personal experience. One of the things that people ignore the most a lot, cyclic polarization test, is

current density distributions. When you run a test, especially when you take your potential start to very, very high voltages, right, and you run that dynamically, you got history problems. Number 1, you are remodeling your oxide to structures that do not exist in the actual application. And number 2, especially when you're at high voltages, the potentiostat is going to source enough current there and what happens when you have a little scratch -- and this is one of the reasons why I oppose that post-test is because you're going to bias that area strongly, especially in the high potentials with high current densities, which you don't see in in vivo at open circuit. So you are causing problems that you don't have in real life.

DR. TAKAI: So I guess that leads in to the question of if you have a covered or a coated device, should you be inducing damage? I think, right now, a lot of people do induce damage through simulated use, so they're not necessarily scratching the device by hand but they'll do, like, a simulated deployment and use the damaged or so-called damaged device at that point.

So could people perhaps comment a little bit more? I think earlier we did have some comments on that. Okay, Larry.

DR. EISELSTEIN: I think Gonzalo is right. One of the things that needs to be taken into account with respect to, you know, damaging a coating on a device is that, you know, obviously you can get extremely high current densities, particularly once you get up to, you know, near breakdown

voltages.

I still think, though, that testing a device in some form in which the coating has been, you know, put through sort of a normal delivery and expansion is important to do because that's going to basically be the condition it's going to be in the body. Maybe not deliberately scratch it, but you should certainly at least expand it to its maximum diameter and deliver it in a delivery tube that might potentially damage the coating.

Now, the concern that Gonzalo brought up, which is that, well, jeez, you know, if, you know, you have high voltages, you have high current densities in these scratch areas, well again, it comes down to how you interpret the results of that test, which again gets you to the issue of, well, if I have a breakdown voltage of, you know, 500 mV, that's significantly higher than what you're going to have in vivo, so it would still be acceptable.

The current density, you know, in those micro-defects that form would be, you know, much higher than it would be if that were uniformly distributed over the surface. But, again, that's why you have to look at this, I think, in terms of the breakdown voltage and what kind of voltage you would have in vivo.

So I think there is a utility in doing some sort of damage, but don't go crazy with it, either. I mean, you can obviously scratch stainless steel with a steel wire and you'll have real problems. But I think that if you strain the device as it should be during deployment, that that's sort of within

reason. And you can still interpret those results appropriately.

DR. TAKAI: Cliff.

DR. WARNER: Cliff Warner from Gore.

I think there's kind of two things I want to comment on here. The first is when we talk about coatings and coverings, I think the range that is at the table today here of what that means to different manufacturers and their devices covers quite a range. And so what may pertain in one area may not pertain in another. So just keep that context in mind when we talk about what might be pertinent for one kind of coating coming off of a post-fatigue test versus maybe something that you might actually consider more of a composite device.

In terms of inducing damage versus waiting for the results from a fatigue test, I think there are a couple things potentially that we should consider with that. The first is fracture coming out of fatigue test is going to be somewhat variable. And so you're inducing into a test method which has some variation a much larger variation from your input.

If you are specifically concerned about fracture and the consequences of that fracture, maybe it is a pertinent way to look at things to induce, simply cut it and create a fresh surface. That may be a much more direct and controlled way to get at what you're actually asking. And if that's the case, maybe that is the more appropriate way to do it, you know, aside from some of the electrochemical concerns that are raised. But still, you're

kind of getting at what you're really, you know, trying to understand.

If there is some more complicated phenomena that you're trying to understand that's a consequence of the actual fatigue cycling, fretting induced damage in the pathways, then maybe you have to go that way. But I don't think it's a simple yes or no in either one, and you have to use the judgment of understanding, you know, what it is you're really asking and use the most effective means to get at that.

DR. TAKAI: I think one of the questions we internally at the FDA had about inducing damage, so for example if you wanted to simulate a fracture, if you took some snips and cut your device, is the repassivated surface the same as if you had a fracture due to fatigue? And the question here is, well, if the repassivation is -- the repassivated surface is different, you know, is the corrosion resistance of that repassivated surface different as well? So that was one of the questions we internally had.

Brian.

DR. BERG: Brian Berg.

I mean, when you take a pair of snips and you cut something, you're going to end up with a highly stressed region of plastic flow right where you snipped it, and that's a completely different metal state. We know that in practice, highly plastically formed materials have different stress or corrosion results than your more virgin material. So I'd be real hesitant to call that a simulated fracture.

DR. TAKAI: All right, before we move along to galvanic corrosion, did people have -- oh, Spiro.

DR. MEGREMIS: I would just say, if that's your question, then I don't think that the post-fatigue F2129 gets to that question or gives you the answer to that question. If you really want to know how it behaves if you scratch it and how it repassivates, then you should hold it at a certain potential and scratch it with something and look at how it repassivates.

And that gets to what Gonzalo was talking about because I did most of those tests for Jeremy for 15 -- 12, 15 years ago. And I did a lot of scratch testing of cobalt-chrome alloys, at least, and one of my colleagues did it on titanium, and I even did it while imaging it under an atomic force microscope. And I can tell you, it depends on what you're scratching it in, first of all, what solution and what potential you're doing it at.

DR. LEMONS: A comment. Listening to all of this, with us not being that involved with fatigue on the stents, but working with a lab that is doing it, I think we're back to the question of simulation. And what experience is showing us is that unless we simulate those events that are applicable to the clinical situation, we're gaining a great deal of data that may or may not be useful.

And as I hear the comments around the room, it seems we're reinforcing that position here over and over again, that if we're going to run these kinds of tests, then we need to be sure what question do we hope to

answer, because if we snip it, all of us know what you do, whether that's with ceramic or metallic or whatever you use for your scissor, et cetera, on and on and on.

So I think we have to ask the question, if we are going to fatigue these under a condition, what particular in vivo condition are we simulating in that fatigue?

And then secondarily, is that particular site, then, one that might be exposed to the environmental conditions that can result in loss of a coating and/or other influences?

So unless we're simulating something appropriately, I think we're testing for the sake of testing, which I like to do because we might like to -- we might answer a question, you know, a new question or get a potential answer, at least have another publication. But I'm not sure that it's relevant to outcome in clinical devices.

DR. TAKAI: Yeah, the point you make hits home for us also because the question of whether even the fatigue testing or simulated use is really representative of actual clinical in vivo environments is a question that I think we all always have. But we're assuming right now, for this workshop, that any of the simulated use testing you're doing is reasonably reflective because that's a whole other workshop in itself.

Spiro.

DR. MEGREMIS: Yeah, I'll just make a brief comment to back up

Jack. I think there is a very big difference between standard testing and trying to answer a question research-wise and what you do in your lab and try to simulate in vivo conditions. And if you look at even the rationale of F2129 where we decided to use deaerated solution, I mean, there's a very specific reason for that, and that was to get consistent numbers and not have the reduction of free oxygen bias that will result.

And so, I mean, surely you could do it in aerated solution, but there is a reason for doing it in deaerated solution. And that's what you get into when you start talking about a standard repeatable test versus doing something in a laboratory, in trying to answer some type of in vivo simulation.

DR. LEMONS: I would just follow up that I totally agree with the comment. But that's the point I was hoping to make. Standardized testing is for standardized testing, and it's completely relevant, completely valuable, worth our time and it should be done, but let's not be doing some type of testing for the sake of testing. It has to be giving us an answer to something that would be relevant to the device or the device application.

And we've seen recently a lot of the testing we have been doing, although very meaningful for itself, really does not represent the conditions of in vivo breakdown, so therefore it gives us a different debris product which has a different bio-reactivity. So, therefore, if we're not addressing the endpoint with what we're doing, then it's just for the sake of

doing it.

Now, that doesn't mean it doesn't screen out materials and isn't a useful test, but we're not going to answer the questions here, you know, in terms of clinical relevancy unless we are sure what it is we're doing.

DR. TAKAI: Valeska.

DR. SCHROEDER: I think, kind of to that point when we're thinking about what to test, I think trying to use a simulation that we think is clinically relevant is one important part and also thinking about what might be the worst case. So sometimes creating a lot of damage to your coating might be the worst case, and sometimes creating a very small spot of damage is going to be the worst case, and so I think you have to think through the coating or the device attribute that you want to evaluate and what might be the worst case for that, and is it possible clinically that that worst case could generate.

DR. LEMONS: Could I respond to that?

DR. TAKAI: Sure.

DR. LEMONS: For example, if you make a scratch on a coating where you do not have a conductive area or if you have the situation you have, what we have seen multiply, the relative area ratio of exposure changes by orders of magnitude. So what that does is it shifts all of the electrochemical and other corrosion information very significantly. So as we're thinking about a standardized test, what we're doing is normalizing the

surface area.

So if you make the next step of then attempting to understand that data, you then have to look at it in terms of what question you hope to answer and is that specific to a certain region or not.

And this has to be device specific because what we try to do in controlled laboratory testing or controlled testing for anything we do in a standard, we try to keep everything as constant as possible, and we do not go back and look at the post-test change in surface area associated with that microscopic event that has taken place because that really shifts your data. But that does not mean that the data you generated is not useful. It is, but it doesn't answer the fundamental questions that go back to the underlying research.

DR. TAKAI: All right. So now to move on and shift gears a little bit. I was hoping we could talk about galvanic corrosion testing. So we asked folks under what conditions you thought that galvanic corrosion testing is needed, and more specifically, whether galvanic corrosion testing is needed if the ASTM F2129 test results were so-called good, not knowing what that actually means, for a single device containing dissimilar metals.

And when we look at the response, half of the folks said yes, you need to consider galvanic corrosion testing even if the F2129 results were acceptable, and the other half were in the maybe and no category. And the narrative responses we got were typically things like, well, the F2129 test

does not evaluate galvanic corrosion, so it should always be considered.

And then, even people who said yes to this also often said, but if the material is close in the galvanic series and your cathode-to-anode ratio is small, then maybe you don't really need to do the galvanic corrosion testing. And other people said, well, maybe, you know, you should nevertheless do it as a confirmatory test but maybe in smaller numbers.

And then the next part of the question we asked was whether or not people thought there is value in doing galvanic corrosion testing of devices of dissimilar metals that are overlapped. And more than half said yes and the rest said no. Some of the yes narrative responses were that if you overlap it with another -- if you think that overlap with another device is likely to happen during clinical use, then it should be evaluated. Some other responses were, like, effects of localized transient behaviors wouldn't be captured, from just looking at the galvanic series, so you should actually do the testing itself.

Some of the no answers stated that there is difficulty in determining, well, what other devices is your device likely to be overlapped with? So what devices do you choose to do galvanic corrosion testing with another device? And sometimes it's also difficult to get a competitor's device to do the testing with. And another couple of people said, well, you know, most of the alloys used in cardiovascular devices are pretty close in the galvanic series, so this probably isn't a concern.

So we also asked generally about best practices and we asked if people measured the uncouple potential before and after. It was fairly split between yes and no, and some people only do it before. And we asked if folks monitor the couple potential, and most people do.

We asked what the endpoint of the test is for galvanic corrosion, and surprisingly most people use time as opposed to steady state current. But I think, from some of the narratives, it seems that people are using time because by 12 to 48 hours, which seems to be commonly used, you already get to a steady state current.

And then we asked folks if people do it on as-manufactured devices versus some other state, and almost everybody does galvanic corrosion testing on as-manufactured devices. And the one no said that they hadn't done the testing, so I wasn't quite sure what that meant.

And we asked about acceptance criteria. So roughly half said no acceptance criteria for galvanic corrosion testing at all. For people who had a numerical value for acceptance criteria for a steady state current, you know, I guess it mostly fell in that 2-4 nA/cm^2 range. And even though we asked for acceptance criteria for steady state current, some people said, well, we use mass loss.

And we also asked about the sample sizes that people use, and the median value was five for galvanic corrosion testing. So we're hoping that people can discuss the utility of doing galvanic corrosion testing. So

consider the scenario of when you have one device with different/dissimilar metals versus doing the testing, anticipating overlap with some other device of a dissimilar metal and if there are any modifications to the galvanic corrosion testing currently being done.

Okay, Shari.

DR. ROSENBLOOM: Shari Rosenbloom.

Yeah, I have a couple of things, a couple of thoughts on this. With regards to the single device with dissimilar metals and the overlap, they're really two different things in a way. I mean, the single device, we know what it is, you know, what the surface area ratios are. The overlapped device, or the potentially overlapped device, creates a bigger problem because, as you said, how do you know, you're looking into a crystal ball, what's going to be in the future and who's -- you know. And we also don't know whether -- what the devices of the future are going to be that are going to be developed that, you know, could be then coupled with this device. But, anyway, I guess what we're looking at when we're doing this testing is what's currently on the market.

I think the galvanic testing is an important piece of the puzzle. You asked about whether it's needed -- if a value is good for F2129. And I think it depends on what we say good is, of course, but let's just, for the moment, say that good might be a wide range of things because there are lot of opinions right now as to what good is.

F2129, as you said, only looks at the pitting, and crevice corrosion doesn't really assess galvanic. And if the device is going to be in contact with another device and the mixed potential that might arise between them might be elevated, then basically that's an F2129 test in itself. You know, you're polarized; you're using one sample to polarize another.

So I think that for the galvanic test, I think it should always be considered. We always have to look at how the device is going to be used, and if there is the possibility that it's going to be put in contact with another device or material, then I think that it's important to do this test. If the mixed potential is high, and we've seen quite high mixed potentials on occasion with galvanic pairs that actually approach the breakdown potential of the lower, the anodic material, you can actually drive pitting.

And so in the case of -- so for a device that might be considered passive on its own, it develops a mixed potential with another material that's sort of high, then I think that you need to do the galvanic test and you need to do more samples.

If the material is just passive, the device seems to do very well in F2129 and you look at it and you look at the potential for overlap and you look at what the mixed potential is, with the galvanic pair and the mixed potential's low, then maybe you just do a couple. You don't have to do so many.

DR. TAKAI: I'm not going to put you on the spot here, but when

you say, you know, you'll suggest to do galvanic corrosion especially when the results are sort of marginal or iffy, what values would you recommend folks do or consider a little bit more to do galvanic corrosion testing in terms of F2129?

DR. ROSENBLOOM: Well, generally, if we -- if one of my clients says that we're going to have a situation -- we'll just stick with the overlap for right now -- where their device is going to be overlapped with another or for sure in contact with another material, we'll say go ahead and do the galvanic and let's do a set of three for that, just as a confirmation that everything is going to be okay, and we would do that only after F2129 was pretty good.

If the F2129 data is low from what we consider -- okay, this is, you know, the way we look at it and for us, that's in the 300-600 mV range, and especially anything that's down in the lower end of that range, that's when I become more concerned about what that couple might look like and what might happen if it's coupled with another noble material, especially if it's got an unfavorable surface ratio for the anode.

So does that answer your question?

DR. TAKAI: Yes.

So I think a lot of people do have pretty strong feelings about, you know, whether or not galvanic corrosion testing needs to be done with another device. I was hoping that people could elaborate a little bit more on their thoughts on the value of doing that, given the challenges.

Larry.

DR. EISELSTEIN: I guess one of my -- and I think Shari touched on this. I'll just reiterate this in a moment. I think that devices made from -- one device made from different materials is a little bit different than the overlap stents issue of different materials.

So to address the question of overlap stents, the question that always came to my mind -- so I don't have an answer to your question, just to -- but one of them is going to be good and one of them is going to be bad. I mean, one of them is going to be cathode and one of them is going to be the anode. Now, so do we expect the manufacturing industry to make sure that everybody's stent that they might get theirs overlapped with, both of those are okay? Which actually, I guess, if I were the FDA, I might say that might be a reasonable approach, but maybe not a palatable one, but a reasonable approach.

But I think it really begs the question of what are we trying to measure in this galvanic test, I mean, what's the endpoint? And, again, speaking with overlap stents, I think that, in general, my experience has been that, you know, you get the steady state currents that are really, really low really fast and that it doesn't really matter. I've even seen the initial anode switch to be the cathode after a while.

And so I'm not sure it's -- with overlap stents, it's a real important test to do, at least based on my experience, and that I would argue

that the currents really probably need to be low enough that either one of that stent pair would be corroding at basically its nominal rate or not much in excess of what its nominal rate is.

The issue now of one device made with two different metals. So, for instance, I think the typical example might be the use of a radiopaque marker, whether it's gold or platinum or something like that, that might be attached to nitinol or something with a low Z number. And in that particular case, it's sort of impossible to do the zero-resistant ammeter-type test on an as-manufactured device because you have to separate the two materials. So, typically, in my experience, when I'm doing those, we recommend that you sort of mask off the radiopaque marker and that you put another similar material that's noble as the other couple at the right area ratio.

Again, do I think that's necessary? Maybe not. But, again, I have seen dissimilar couples primarily through a coating operation in which you have come up with a severe enough galvanic couple or maybe a metallurgical condition that actually predisposes the device to a very low breakdown. And in that you could determine with an F2129 test without even doing the zero resistance ammeter test so long as you damage the coating enough so that you could see that you have a problem.

DR. TAKAI: Brian.

DR. CHOULES: Brian Choules.

The metals that stents are being made of, and the vascular

devices, we understand what their rest potentials are, and what their corrosion potentials are, and they're really very close in the galvanic series. So it just doesn't seem to be an issue, as well as, you know, in the vascular world, these different materials get used all the time and, you know, we've seen explants and we just don't see an issue in that way.

So I agree that with overlapping stents, with the materials that we have today, it's just not an issue. Now, when you go to radiopaque markers where you're using noble metals, there might be more reason to be concerned.

DR. TAKAI: Jack.

DR. LEMONS: Just a moment on the details again. Well, this comes from a variety of literature, not always specific to stents. But if you're mixing titanium or titanium alloy or nickel-titanium with iron and you're coupling, what you're going to have, initially, because of the properties of the surface and the kinetics of repassivation being very different amongst those two, is initial reaction where that environment changes because of the first reaction products to the titanium, that immediately alters the environment with the steel, which makes it susceptible to the breakdown and the corrosion and corrosion products.

If you place cobalt and steel together, you have the reaction where what happens to the cobalt is very specific to the distribution of the molybdenum included in the alloy and the conditions that that alloy has been

prepared under. And once again, you get an initial environment that will leach to a secondary environment.

The third one that you get involved with is the cobalt and the titanium, where your initial data will tell you that they're very similar. However, in the initial breakdown product, you get a secondary product, which is primarily related to the secondary phosphides from the cobalt that leads to a different environment that leads to preferential corrosion, then of the cobalt alloy, depending upon the alloy chemistry, grain size, and other characteristics of the alloy.

So what I'm attempting to say, if you're going to do testing, you need to really do testing that relates to what might happen in vivo, and I suggest that the testing that we're doing here, although valuable in and of itself, is not necessarily representing what might be the condition under galvanic coupling and fretting, which is usually associated with some type of microemulsion.

So as we have analyzed these interfaces and looked at the electrochemistry, you can also get a flip-flop in terms of the anode/cathode relationship. So it gets very, very complicated. And if you get a polymer coating on one of the components and if the underlying substrate happens to be a steel which is subject to crevice corrosion at low oxygen tension, it all changes again.

So I think the details are quite important in terms of what

you're asking for, and you may be asking for two years in research projects to even get close to an appropriate test. I don't think, personally, we know enough about it, in general. And a lot of the information we have developed really hasn't been confirmed by others, and I think it would need to be before you would accept it in the community.

DR. TAKAI: Maybe I'll ask -- I'll go back and ask the more simpler question rather than the overlap of dissimilar metal devices. So going back to the question about, well, if you have a device primarily made out of one metal and then you have something like a marker or different components of the device that are smaller, made out of another more noble metal, whether or not if you do F2129 testing and the outcomes were acceptable, whatever that means, whether at that point do we need to be asking folks to do galvanic corrosion testing as a confirmatory test, or is it okay to just look at the F2129 test, given the difficulty and like, especially if you have smaller geometries to mask off that other piece.

Shari and then Larry.

DR. ROSENBLOOM: With regards to the stent with markers, that's a situation where often cases are usually the stent is going to be the anode because the markers are so noble. And, of course, that's the worst galvanic pair you could make but with the most favorable geometry because you've got such small markers.

And so what we've primarily found, when we've taken a look at

this is that if the device as a whole did well in F2129, we'd run the galvanic. It's not a bad idea to run the galvanic. Maybe not too many samples, but just as a check to make sure that there isn't anything going on there that we ought to know about galvanically. But usually, we get very good results with that.

The concern that I have is when you might have a device, a single device maybe, made out of also two materials where one is incredibly noble, not a stent with markers, something different, but that noble material is much larger, has a much larger surface area. And that's where I have a real concern and where I think the galvanic testing is very important to be able to be sure that that unfavorable or potentially unfavorable surface area ratio between anode and cathode with a very noble material there won't drive the other one into corrosion.

DR. TAKAI: Larry.

DR. EISELSTEIN: I don't disagree with anything Shari said, but the point I'd like to make is that I don't think the F2129 test really addresses the galvanic couple. In effect, the galvanic test is imposing -- I'm sorry. The F2129 test is imposing various potentials in a continuous fashion up until you reach breakdown.

What a galvanic test is doing is it's saying I'm going to impose a constant potential, whatever the potential difference is between your noble material and your stent, for instance, if it's a marker, and therefore, it's really

sort of not testing.

And it's actually that 2129 test that tests what it tests, which is the breakdown voltage and the -- in its particular resting case, its rest mixed potential, but doesn't really -- now, what it can do is that, for instance, if there were a metallurgical change, for instance, between the, let's say, like, inner diffusion of gold into the nitinol, that's a whole new story. And then the F2129 test would be able to determine whether or not that had caused a significant breakdown in the inherent breakdown potential for that material.

But simply if it's, you know, crimped on, you really have a crevice in a potential, and if you really wanted to evaluate that, I think that you have to either do the separate F2129 test, or an alternate approach would be the -- you just put it in the solution that's aerated and leave it there for, you know, a month or two and see whether or not that inherent couple in the in vivo-like environment would eventually cause any pitting or degradation as a result of that.

DR. TAKAI: Jack.

DR. LEMONS: I think here it's worthwhile looking at the long-term experience in dentistry when you asked a question of noble alloys. The golds, paladiums, platinums have been used extensively and coupled with a multiplicity of other alloy systems.

In general, in the absence of fretting but in the presence of a crevice, you're going to see that the nickel-chromium alloys and the partial

denture alloy of cobalt, which was used previously in dentistry and continues intra-orally, and the steel will break down significantly when you've got a potential difference or you've got a galvanic coupling.

However, if you looked at the very long-term results with titanium and titanium alloys, in general, when coupled with more noble materials, the characteristic of breakdown in the absence of fretting has not been significant in that environment. So even in the presence of using some fluoride rinses or other things that may alter the local surface conditions on the titanium, it still appears that that's not a significant issue.

So I think, once again, it's sort of necessary to look at that combination in that circumstance of actually the application that one is considering. And I realize this is not necessarily relevant, but I think it's sort of information that might be useful.

DR. EISELSTEIN: Just one question on that. When you're talking about titanium, you're talking about, like, Ti 6-4 or something like that as -- or titanium and not necessarily nitinol?

DR. LEMONS: Yes, sir.

DR. EISELSTEIN: Okay.

DR. LEMONS: That very limited information on the nitinol, and the nitinol that was used for dental implants, which was done in the international theater pretty extensively, was really altered significantly by electrochemistry to get away from the issue of potential of nickel and nickel

hypersensitivity. So, again, one would have to look back at how those materials were manufactured.

DR. TAKAI: Valeska and then Shari.

DR. SCHROEDER: I guess thinking about galvanic corrosion, I like to start just by the literature values of couples and looking at the galvanic series in kind of an assessment of where you are on that series to start to think about your risk, and based on that, you can make additional decisions. I mean, we're usually doing that when we design the device to begin with; that's why we're looking at things that aren't too dissimilar.

So I know Shari mentioned having a galvanic couple where you see differences in potential that would drive breakdown. I would say, typically, we're not designing anywhere near that; we're designing at the nanoamps that people were, you know, talking about on their acceptance criterion levels. And I think there you're considering, when you have two dissimilar metals on the same device, as soon as you separate them, well, you're giving away the idea of testing your device.

And so I think the immersion test or something like that can give you a better assessment. I actually think you do get something out of F2129. If you have a problem or are creating damage or have something unique going on at that interface, you can get information out of that as well. But as soon as you separate in your testing, you know, a solid metal that is your marker in the device, you've lost the uniqueness of your device.

DR. TAKAI: Shari.

DR. ROSENBLOOM: I just wanted to mention one thing. You had a slide up earlier about methodology of the testing and what people do, and I saw that there was a range of how long people did this galvanic test for.

One of the things that I think this test does give us the opportunity to do is to monitor things for a little bit longer and take a look at some of the transient behavior. If there is going to be problems, it may not show up right away; it may take time, it may show up at intervals.

And so I would just -- I would be a proponent of having a test last probably at least 24 hours, I'd say, for just looking at the -- it says 12 to 48 hours. Practically speaking, if you started testing and you're going to run it for 12, you might as well run it for 24 unless you've got some poor lab technician who's in there all day long waiting to take that test down.

And just because we have seen times when things seem to be going along quite well and you know, 8, 10, 12 hours into the test you get a spike and you get something going on, and I think that's part of what this test is trying to assess.

DR. TAKAI: All right. So before I close this corrosion session, did anybody have any last comments?

(No response.)

DR. TAKAI: All right. So we'll be having our Surface Characterization session. We'll start at 3:15.

Thank you.

(Off the record.)

(On the record.)

DR. DI PRIMA: And we are prepared to start the Surface Characterization session of this workshop.

We were able to scramble during that break and we found a replacement speaker, so you guys will get a more interesting intro to this session than we were looking at.

And sorry. Real quick, my name is Matthew Di Prima. I'm going to be one of your co-chairs along with Dave Saylor.

And with that, I'd like to introduce John Moskito from Evans Analytical Group, and he's going to give a brief overview on surface characterization.

MR. MOSKITO: Thank you, everyone.

Now, these are slides that I present in a day-long course on surface characterization. My company is a test house. It does testing on the very surfaces of materials, semiconductors, medical devices. I'm very familiar with nitinol and stents, in particular. But this is a big presentation, so I'm going to be jumping all over the place, trying to make this a 10-minute presentation. So with that, let's kind of go on here.

Okay. SEM/EDX. We'll start with the very basics here. So we're up here at the top, SEM is an imaging technique. It also can be used

with EDX to give us elemental composition. Let's see. Oh, let me describe our bubble chart.

So this the famous EAG bubble chart. What this is, is a description here, on the X axis, of detection limits -- excuse me, X axis of detection limit -- oh, sorry, Y axis detection limits going from percent levels at the top down to parts per million, parts per billion, parts per trillion. Here on the X axis is the analytical spot size. And the analytical spot size is the X-Y diameter of what you're looking at.

So it goes everywhere from centimeter sized analyses down to A level analysis. And within that, within the box, are the analytical techniques that will allow you to look at elemental composition with a spot size given by the X axis.

So it will go everywhere from XRR, which has a 1 cm sized analysis area, through XRD, XPS or ESCA, which is down there at about 20 µ spot size; SEM/EDX at 1000 A for elemental composition; auger, down here, going down to about 1000 A. And then when you need to get the ultimate resolution, TEM, EDX using TEM.

So within here, we can look at different sized areas, and you can see it's very applicable because with finished devices, we're usually dealing with sizes that run somewhere between 30 µ wide to 6 µ wide areas that we need to look at. So we can use a number of these techniques to characterize the material.

Let's see. Oh, we go down here. There we go. Okay, so for SEM, anytime you really need to take a picture that's beyond the imaging capabilities of an optical microscope, it's indispensable for characterizing the surfaces, doing failure analysis. It's a great way to look at deposits, particles, pits, et cetera, and combined with EDX or EDS, energy dispersive spectroscopy or energy dispersive x-ray -- it's two different names for the same technique -- you can measure the elemental content. It's a parallel imaging and elemental detection technique. They're two techniques put into the same instrument, so it was very fast, very inexpensive. I would imagine every single one of you has one of these in your lab. So very powerful, quick and easy to use.

Accuracy depends upon application. Basically, electron gun going down, very focused beam, hitting the sample with the detector off to the side to detect the image.

Let's skip this.

Analytical volume. So we were just talking about, in that bubble chart, about X-Y spatial resolution, how small can I get? Well, we all have to remember, especially when we're doing surface characterization, is how deep am I looking?

So what we have here is the incident electron beam coming in, and there's a volume of how deep the electrons go in. They create this pear-shaped volume, and from in that pear-shaped volume, you can get many,

many different things. You can get secondary fluorescence, you can get characteristic x-rays, you can get backscattered x-rays, you can get secondary electrons for imaging and you get auger electrons, and you can get photoelectrons for XPS. All of them come from different depths. And you can then, with some techniques such as EDX, you can change that depth of analysis by changing your experimental parameters.

So, in general, this volume here is the volume that you've analyzed with EDX. Your electron beam, it can be 10 nm in diameter. You know exactly where it's going in. But once it goes in, it scatters and your EDX analysis volume is dependent upon the energy of your beam. It can be anywhere from 1000 A in diameter and a 1000 A deep to 2 µ diameter, 2 µ deep.

So depending upon the energy you're using, and you should select it for the depth that really matters to you, then you can get the data that you're looking for.

In comparison, the surface -- what I consider surface-sensitive techniques, auger electron spectroscopy; XPS, x-ray photoelectron spectroscopy, also called ESCA, these are not limited by the incoming beam, but by the escape depth of the photoelectrons in case of XPS or the auger electrons in the case of auger. And they're limited to very, very surface-sensitive analysis volume, typically on the order of 30-50 A for auger and 50-100 A for XPS. So orders of magnitude different from EDX. So you're going to

get, when you compare EDX data that you may have taken in-house to XPS or auger data, they may say very different things.

Let's see. EDX detectors, the parallel detectors. They're a survey technique. And all these techniques that we're talking about today in these next 10 minutes are survey techniques, meaning you don't have to know what you're looking for. You can put the beam on your sample, on your defect, on your particle, on your pit, and it will tell you everything that's there within the elements that are detectable by the technique.

And for all three techniques that we're talking about today, EDX, auger, XPS, we're talking about everything except for hydrogen and helium for the most part. So pretty much everything in the periodic table.

Let's see. Well, let's skip this part here.

Okay, secondary electrons. Just basically, we have some pretty pictures here. Has a great depth of field, great imaging capability. We talked earlier about imaging to look for pits, to look for differences in composition. Here's a graph of -- most SEMs have different detectors on them. Most of the time, we're looking at secondary electrons. This is primarily the contrast mechanism for secondary electrons. It's primarily topography, how rough is my sample. Is that bump that I see, it's an innie or is it an outie?

The other detector that you can use for imaging is backscatter. In this case, backscatter will give you a deeper look into the material, slightly deeper. But its primary contrast mechanism is Z number. So if you want to

look for differences in near-surface composition, a backscatter picture is worth a thousand words. In this case, we can see these two images -- well, excuse me. The backscatter image that we see on top is an exact overlay of what we see in the secondary.

So you can see very different information is gathered from the exact same sample using different detectors in your instrument. And these are detectors you have on your instrument right now. So knowing how to use your instrument is going to -- can reap a lot of benefits.

In this case, these pictures here, the bottom one is one of topography, the secondary electrons. The top one, backscattered. It's showing an aluminum matrix with zirconia particles and zirconia enrichment at the grain boundaries.

Let's see, EDX. So we saw some EDX data earlier. One of the things about EDX is that you can modify the depth of analysis by changing the beam energy. So remember that pear-shaped volume that the electron beam scatters into; by changing the energy of the incoming beam, you can either make it more surface sensitive or you can drive it in to look at the bulk compositions.

So here we have two looks at the same material, one at 3 kV incoming beam energy and another one at 10 kV. And in 3 kV, you're much more surface sensitive. You're up near the surface, you can see. In this case, it's a semiconductor, aluminum lines on silicon. You can see the aluminum

lines, you can see the silicon from underneath the line because it's still going kind of deep. But you also see the surface materials, the nitrogen, the fluorine, the oxygen, the carbon that's on those surfaces, so, again, surface sensitive. By going into a stronger beam, a 10 kV beam, now you're blasting through that near surface and now you're looking at the aluminum metal itself.

So how you run your instrument is going to be very key. What kind of data do you get? Am I looking at my modified surface, my oxide surface, or am I looking at my bulk material? It can be very, very different, and the more powerful the beam, the deeper you're looking.

EDX spectra can also do maps. Because it's a scanning beam going across the sample, you can now take that EDX data and specifically look for, let's call it, iron, down here. And you can look for iron as a function of X-Y position, and then you can generate these maps so you can see that iron, where it's brighter, is where there's more iron in the material. And, again, you can do the same thing with your devices.

Let's see. Most of this we're going to not talk about because it's not applicable.

Okay. Yeah, let's try this one here and then go on. So, again, depth of analysis here. We just threw on some iridium metal on a glass slide. Depending upon your energy, again, at 10 kV, you see the iridium peaks, and underneath the glass slide, the silicon, oxygen, the calcium of the glass slide.

At 20 kV, you barely see that 500 A thick layer.

So I can't stress enough, you know, changing of your experimental parameters can change how deep you look.

Again, imaging rapid elemental maps is a benefit of SEM/EDX. So you can get the image that you're looking for, and by using EDX and the mapping capabilities of your instrument, you can find out where is it heavy in carbon, where is the phosphorous, where is the oxygen, where is the nitrogen? These are the benefits of being able to map and selectively say, you know, is this residue the same as this residue over here, yes or no? So it can be very powerful.

Okay. Well, let's do the summary too, then, since we're right here. Okay. Strengths: relatively fast, simple to operate. You probably have one in your own lab. Image resolution: the best ones go down to 10 A resolution. Combined with EDX, you get imaging, you can get -- with backscatter, you can get contrast imaging for elements and you can do EDX for elemental identification and mapping. And it's a great first look because it's typically considered a nondestructive technique. As long as your sample is able to withstand the vacuum of the instrument, which is typically on the order of about -5 torr, it comes out at exactly the same state as it went in at.

Limitations: imaging may spoil subsequent analyses; -5 torr is not very clean, so other surface sensitive techniques like auger, like XPS, like time-of-flight SIMS, they're going to be compromised by the dirtiness of an

SEM chamber.

Quantification of the EDX data is sample dependent. The sensitivity factors that are used have a certain number of assumptions made, that it's a bulk material, that it is very similar to the standards that it's used against. I'll just leave it at that.

And then third, interaction volume may affect result interpretation. Again, the higher the beam energies, the deeper you look, so you need to know how deep you're looking. And samples may be vacuum compatible.

Let's go. Much more surface sensitive is auger electron spectroscopy. Again, here with the bubble chart, we're here in the sweet spot for medical devices. We have percent level detection limits, percent levels, not parts per million, but percent levels. And we have spot size that is down to about 1000 A in diameter. That's for the newest instruments. It is more -- let's see, let me go -- sorry, I'm on the fly here.

Key applications. Smaller analysis is where auger shines. It habitually goes down to 1000 A sized analysis areas very easily. The oldest instruments still have a spot size of about 1 µ. So very small analysis areas and also coupled with very, very shallow analysis volume. So for SIMS that are too thin to see by EDX or when you want to look purely at the surface of your materials, auger and XPS are going to be much superior to EDX. And then for thin SIM analysis of volume, we can do depth profiles and it's

quantitative.

So, again, with the analytical volume, it's an electron beam technique just like SEM/EDX. We have a very focused electron beam; we're driving it in deep into the sample. We still drive the electron beam 1 μ, almost 2 μ into the material depending upon beam energy. But unlike EDX, where you're getting x-rays from EDX through this entire volume, you're now only generating auger electrons that can escape and reach the analyzer from the top 30-50 A, so orders of magnitude more surface sensitive than EDX.

The other advantage of auger is that even though it's creating this volume of excitation with the electron beam, because it's a different mechanism to get these augers out, it's electron beam energy agnostic. It doesn't care whether you're using a 3 kV beam, a 10 or a 20 kV beam. So you can use the most powerful beam you want to get the information, but it's still only coming from the first 30-50 A.

Yes. Okay, let's not go there. Let's see. Description of technique. Electron source at the top, it's an electron gun just like an SEM. It comes straight -- well, it doesn't come exactly straight down, but it comes down to the sample, creates auger electrons, the auger electrons fly up, they go through an analyzer and hit a detector.

In the case of the instruments that I use, it's a ray detector, meaning it sits -- the electron beam is coming straight down, the detector for the instrument surrounds the electron beam. The advantage to that is what

you see, you can analyze. So there's no issues with having blockages where you have an incoming beam coming in from one direction and an analyzer in another. This can be one of the limitations for XPS and always can be a limitation for EDX if you have a highly structured sample. So it can be some consideration there.

Let's see. So what does auger data look like? Basically, the raw data is the green trace with the rising background. Traditionally, it's been differentiated. So what you get is a flat background with peaks at particular energies, and the energy peaks are indicative of the element that the electron beam hit. So we see, in this particular one, aluminum, fluorine, oxygen, carbon, sulfur. And the relative intensities of these peaks, very similar to EDX, can give you quantification.

Here's just some pretty pictures. This is a big, whopping -- oh, I don't know, 100 nm, 1000 A sized particle. We can go in there very easily and analyze the particle, analyze the background. Just like with EDX, apply maps but again very surface sensitive relative to what EDX can do.

Let's see. Even when it's too thin to see by SEM. So SEM, you always think it's looking at the surface, but it actually looks about 100-200 A into the material. And so even samples that were residues that are too thin to actually see with an SEM, you can actually, because the analysis volume is only 30 A or 50 A deep in auger, you can actually very easily see the contamination and map for it, get elemental signatures that are very different

on the residue versus off the residue. So, again, a very surface sensitive technique even when it's too thin to see.

Yeah, this is probably relevant here. Grain boundary precipitation. In this case we're looking at inside pits, inside occlusion. We're looking at occlusions. It can be very powerful when you need to keep that analytical volume very, very localized, both in XY diameter and also in depth, in Z.

And here again are just some more pretty pictures.

Okay, you can also do a depth profile. We're still only looking at the first 30-50 A when we do the analysis, but with an additional ion gun, you can erode the surface, basically dig a hole. And then you look at the hole, the bottom of the hole again, and you dig a little deeper and you look again; dig a little deeper, look again. And what you get, after all that, is a depth profile. And you can get composition as a function of depth.

What this also does is look at the composition of that surface layer that you've created, look at the thickness of the oxide, look at the presence of any contaminants within the material itself, and compare them: good versus bad, predicate versus your device, Process 1 versus Process 2.

I have here some data that I'm able to show. So normally, I have a test house, and normally, I don't talk about anybody else's data. I don't even tell you who I work for. But in this case you would've seen this data today, anyway.

So what we have here is a nitinol sample with an oxide layer on it. Unfortunately, because of a test house, I can't talk about the reasons why it looks like it does, and so I'm hoping that some of you here today can help elucidate why we see, in this case, you know, a double oxide or even, depending upon how you move your thumb, a triple.

And so this is what auger is able to do for you, is give you a composition of that oxide or that near-surface composition as a function of depth. So here we can see the strongly titanium oxide layer, which we typically see and in this case, underneath, a nickel-rich region and a nickel-rich -- well, it's a nickel-titanium oxide within the region and then going in eventually to the bulk composition.

So this is, again, a very powerful tool that EDX would not be able to do. And if you see here, you know, the depth of analysis is many, many data points within that first 800 A of that oxide. So we can see very fine changes within the material as we go in. And if you notice also contaminations, potentially, of sulfur or other contaminations.

Okay. And you know what? Since I don't have EDX data on me, I think we're going to wrap it up right here. So any questions?

(No response.)

MR. MOSKITO: Okay. Thank you very much.

DR. DI PRIMA: Thank you so much, John, for coming up.

(Applause.)

DR. DI PRIMA: Erica, which PowerPoint are we -- thank you.

All right. Well, we just had our talk, it was not by Christine from NDC, so we will jump on to Objective 1, Homework and Discussion. We've allotted about 40-45 minutes for this.

So the first objective in the surface characterization homework, we asked everyone to identify commonly used methods for surface characterization of metal implant devices. We then asked them to describe the benefits and drawbacks of current surface characterization techniques, and then we asked whether surface characterization is needed in general. And our goal is really to find out what people were using, what worked for them, and how much they felt that it was needed.

So a brief overview of the responses when we asked people what they were doing. So we had 17 responses, and so it's originally broken down by technique, and we then lumped it into technique type, so that's how we can have 17 responses for surface characterization or, sorry, surface chemistry.

So, roughly, where people are doing about equal amounts of auger to XPS, we're seeing a large response to SEM and a few people are doing more depth profiling and the numbers are really too small for us to decide which technique is preferred.

So when we break this down by alloy, we had nine responses involving stainless steel. Again, we see that SEM is heavily favored. Auger

and XPS is split. And we had one person who performed depth profiling under the stainless. For cobalt-chrome, again, SEM heavily favored, some surface characterization and one depth profiling. And then, nitinol was the more exciting one for us. Again, we can see that SEM is heavily favored. We see a lot more surface chemistry being performed, again evenly split between the two techniques, and significantly more depth profiling. So yes, people are doing this, so we were happy to see that.

So the next question was do you do this in-house? So the first pie chart, the question was do you contract out any surface characterization work? So we had 14 responses, and 85% of the respondents contracted out some of the work. So only 15% performed everything in-house.

The next question was do you perform the technique in-house? So we went technique by technique where it was stated to see what fraction people performed in-house. So here, 21% of the respondents performed the techniques in-house, with 79% of the technique being sent out. So that's telling us that you guys are sending most of your work out, which made some of the follow-up questions about what parameters do you run or -- well, we got a lot of blanks.

(Laughter.)

DR. DI PRIMA: So when we asked about technique limitations, for auger, small spot size was mentioned a lot because it's so surface sensitive, coatings as well as surface roughness and contamination can affect

your values. And complex geometry can mask regions. For XPS you had very similar concerns. You have the low spatial resolution. The coatings, again, can make it difficult to characterize surfaces. Some people discussed issues with sample sizes and holders and needing to cut down parts. And yeah, you can read some of the other ones.

So SEM, everyone pretty much said the same thing, and it's well enough known that we figured we'd just move straight on to the depth profiling. So with FIB/SEM, we had three, sort of, general concerns being noted: does not provide information with regards to composition, does not work on thin oxides, and it only covers a small area.

And then sputtering with either auger or XPS, several people noted that this is -- it's calibrated to soak in dioxide, which sputters slightly differently from the titania, so that's a potential source of air. Again, it only covers a small surface area. And someone was kind enough to point out that it cannot be used alone to predict corrosion.

So when we were looking at the general oxide thicknesses, we're comparing the two depth profiling techniques. We had very similar responses. So with the sputtering, the range across five responses was 2.8-120 nm. With FIB, we're seeing 2.3-168 nm across three responses. And using auger or XPS, you're calculating the thickness by full width, half max of oxygen peak calibrated to the Silica standard. And with FIB/SEM, you're actually measuring the thickness of the oxide that you've just cut.

So the question we then asked was do you think surface characterization testing should always be performed, which since we had "always" in there is a little bit of a loaded question. But 31% of you said yes; 69% said no across the responses. And most of the noes recommended performing surface characterization at some point in the life cycle, primarily R&D.

So then we asked when should surface characterization be performed? There is general agreement that it should be performed when some sort of results from the performance testing is questionable. You have a little breakdown, you're seeing more nickel leach than expected. If you do some process change that can impact the surface, and is part of the process in device development step. Some dissension on whether it should be used for process and device validation along with routine process monitoring.

So our discussion questions. The first one is going to be when should these techniques be used but currently are not? Conversely, when should these techniques not be used but currently are? And once we've hashed that out, hopefully, we'll discuss, have you observed any device characteristics such as geometries that are problematic for a specific surface characterization technique? And then we'll end with Is there a general role for surface characterization in process validation and monitoring?

So John, since you just gave us such a wonderful talk, do you want to discuss your thoughts on the first point about the use of the surface

characterization techniques?

MR. MOSKITO: Well, as a service laboratory, I don't think I'm really qualified to say when they should be used because I am very, well, very much removed from the actual correlation between the information that I provide to my client and the rest of their data. So, you know, in my personal view, I think it should be yes and always, but --

(Laughter.)

MR. MOSKITO: -- I don't know. I don't have a good answer for that because I don't know what my clients do with their data.

DR. DI PRIMAR: Yes.

DR. SCHROEDER: I guess I would say this is a little bit general, but they should be used in collaboration with the functional assessment, so I think the surface characterization is only meaningful when it's correlated or compared to something else.

DR. KRAMER-BROWN: Pamela Kramer from Abbott.

It's kind of a loaded question. You're asking, when should they be used where they're not; conversely, when should they not be used where they are? And per what the answers were that you showed, at some point in time, you should know what your device is, you should fully characterize it and, as Valeska just mentioned, use it in collaboration with functional testing, the functional understanding of your device. So I think it's a hard question to answer, I'll be honest with you, of when should they be used but they're not?

I think people use different techniques to assess their device at some point in time during the life cycle, be it during R&D or be it to submit data with the filing or both probably. I can't answer the questions that are there, but I can tell you, it does need to be done, at some point in time, to the satisfaction of both the person who is assessing the device or the organization that's assessing the device and the regulatory body.

DR. KAMMER: Yeah, I just want to say that especially like in the morning when somebody was asking that they had like, you know, E_b-E_r, they have high values for E_b-E_r and at the same time they were observing high nickel leaching, and in some of their samples when they had low E_b-E_r and they were also low leaching.

So at that point, I think it's very critical to do like surface chemistry analysis, especially with XPS, to find out that although E_b-E_r was high, which probably means that oxide was very, you know, probably thick and very stable or uniform, but that contained -- that probably contained a lot of nickel ions, and most probably they were in the metallic form, and that's why they were leaching out. And at the times when there were low E_b-E_r values and at the same time there was low nickel leaching, so which probably says that, you know, like, surface characterization should be done to find out whether the nickel, most probably when there was no nickel leaching or low nickel leaching, which means that nickel present on the top surface was in oxide form.

So I guess it's kind of critical when corrosion analysis or, you know, ASTM F2129 is not really answering the question, then, I think, at that point surface analysis is very important.

DR. BERG: Brian Berg.

I mean, the way I look at it is this is an analytical technique to help you understand why, but it's not really a useful test for telling you what happens. And so if you need to understand something because you have a problem that you're trying to understand or you're doing something very different and you want to understand the mechanisms, it's useful. But in terms of typical regulatory submission in terms of performance, it's a secondary add-on piece of information rather than more fundamental how does it perform information.

DR. DI PRIMA: So when we review or if we have feedback or provide feedback, we can't really tell you which technique to perform. We can only say we have a concern about their oxide thickness layer. So sometimes we get responses back where people ask, well, can I use some crazy technique, we have to go essentially to Wikipedia to see.

So the sort of intent of this question was, you know, are there some analytical techniques that you want to use but, you know, haven't been or --

DR. SAYLOR: Yeah, I guess -- Dave Saylor, FDA -- if you want a specific question, when would you use, say, XPS versus auger for depth

profiling, for example, are there any specific examples like that where you would prefer one method over the other or vice versa?

MR. SCUTTI: Jim Scutti, Atrium Medical. I wasn't signed up for this one, but I'll sit here anyway.

Yeah, as far as analytical techniques, XPS tells you something about the compounds that are there because it has binding energy as the data output. Binding energy tells you about what the -- you know, whether it's an oxide or it's what the valence in an oxide is. Auger is elemental in nature. So they both give similar data in terms of being very close to the surface, but they give you slightly different data that may or may not be necessary to do both of them, but if you do both, you get a bigger picture of what that oxide is comprised of.

In terms of what analytical tools not to use, I think we need to be -- we need to caution ourselves not to go too far with the fancy tools that we have. SEM/EDS is ubiquitous and it's a great tool, but it's limited. And to think you might be able to deduce some nickel leaching data based on EDS analysis of a corroded surface, you need to take that with a grain of salt because of the things that John brought up in terms of the volume of the material that you're analyzing, the fact that you're maybe, you know, 300-400 nm deep in that sample or more, but the oxide layer that you really want to analyze or the denuded, nickel denuded region at the surface is so much thinner than that that really you're not going to be able to get good data out

of that, plus EDS isn't very quantitative for the reasons that John mentioned as well. So thank you.

MR. STORMENT: Chris Storment, Medtronic.

One question or one point to be aware of, though, is when you're doing the depth profiling, you do scramble those oxidation states. So, you know, as long as you're just looking at the surface, yes, you can extract the valence, but if you start doing the sputter depth profiling, you will lose that.

DR. LEMONS: I'm not sure if I'm in this session or not, but I'll participate.

(Laughter.)

DR. LEMONS: With regard to imagining and doing that on a routine basis with regard to device analysis, retrieval and analysis, we always start with optical. And we have found, more recently, that the new systems that are available where you can add the digital capability, the key-in systems and others, are extremely valuable because you can go from low to high magnification with a single unit and you can handle parts or you can do things that you would not do otherwise.

As soon as we get to a question where we're asking about depth of field or imaging what might be there or not, that moves us immediately to the SEM, and the new environmental systems are a lot more valuable to us in that regard because we can deal with a wide range of

excitation voltages. But we can do them, as is said, elemental chemistry, to a limited degree, if you understand the limits of it.

All of our XPS auger spectroscopy, all of those types of things, Raman spectroscopy, FTIR, all of those analytical techniques, we normally develop a separate specimen for that to simulate what we would see because we find it very difficult to prepare a specimen from a device to maintain the conditions because the elemental chemistry changes that come with handling or processing.

So, in general, with regard to a device, we'll only do that from a research laboratory standpoint where we're talking about elemental structure or elemental chemistry at that surface with some modification or alteration. So most of what we do is optical and SEM, although we do the other things routinely also. So they all have their value.

DR. DI PRIMA: Thanks for that. I see some -- or some tents are up.

DR. MEGREMIS: I would just add the caveat that -- oh, Spiro Megremis from the ADA -- that you have be careful when you start comparing corrosion data with any type of auger electron or any type of quantitative data where you get something about the oxides, because I think if you look at electrochemical impedance spectroscopy, which will tell you something about the thickness of oxides at different potentials, et cetera, and then you take that same material and you put it in a vacuum and you look at

the oxides with auger or something like that, you'll see they don't correlate and so -- which I know a lot of the people would do that, understand that pretty well, but some people don't always get that.

DR. KONSTANTINO: Eitan Konstantino.

We're using mainly experience in auger and this chart is nice. The profile that John showed might be one of ours. Anything that -- work with evidence and we're using these methods to develop and qualify our processes. For example, when we worked with stents, we wanted certain -- in the oxide, so we used a catheterization to give us feedback on the oxide.

And with nitinol, we used the auger depth profile to develop this unique depth profile, unique oxide at the junction. Others may be doing the same, but we find it very important, and I generally believe that you need to know what you are putting in the body.

So corrosion testing is one thing that you should do and we are doing, but it is limited to the scope of the test. That's my view.

MR. MOSKITO: Just one thing I wanted to add about the analytical techniques also is yes, I didn't get a chance to talk about XPS, but it gives you chemical state and it give you surface sensitive chemical state. The downside of XPS is that it has a relatively large spot size on the order, in general, of about 1 mm in diameter, so much greater than the strut size of a stent. You can look at the overall stent, looking at many struts across, or the entire stent itself, to get the chemical state from the surface, but it's next to

impossible to do a true depth profile. So you can't produce the oxide layer of thickness using XPS because it doesn't have the spot size capabilities.

Auger, on the other hand, doesn't give you the chemical state, but it has the spatial resolution and the surface sensitivity to give you that oxide layer of thickness and the composition as a function of depth.

So they are used very differently, XPS for surface chemistry and oxidation states, and then auger for the oxide depth profiles. And concentrations as a function of depth. So for medical devices, you use them very, very differently.

DR. DI PRIMA: Okay. That's very informative. So we will move on, then, to the next point. Have you observed any device characteristics or geometries that are problematic for surface characterization? So I know, with some stents, especially the laser-cut ones, when you get into some of the little grooves, you get really weird areas, sometimes, of the heat-affected zone, and I would imagine that getting in there with an auger beam might be difficult.

So in your experiences, are there any sort of device characteristics like that, that have proven to be especially problematic for you to perform surface characterization on?

DR. KRAMER-BROWN: Pamela from Abbott.

As a metallurgist, I could say there are always ways to get around any issue of not being able to see something. For example, you can

pot and polish your sample and cross-section down to get a cross-sectional view of what you're trying to look at. You can do different angles of polishing on something to make the effective area that you want to look at bigger than it is in an orthogonal view. So there are ways to get around things that are difficult to look at.

DR. LEMONS: A comment. Jack Lemons.

As we have been attempting to pre-corrode stents for evaluations, the assessment of changing the surface area and controlling the type of corrosion at the surface really can only be determined for the experimental systems by microscopy. And the critical part about that is you need to look at all of the features in all of the areas on the stents because we see preferential and differential pitting corrosion depending upon where we are on the particular structure. So, therefore, we find it very difficult to do this and especially to do that non-destructively if you hope to use that stent for something else, like implantation in a laboratory animal.

So the key to all of this, I think, is that the structure and characteristics of stents, at least in our hands, has made them extremely difficult to image routinely for all of the surfaces and features that are there in the different designs.

MR. LASLEY: Chris Lasley with W. L. Gore.

Yeah, I think, like Valeska and Brian mentioned, it's a great tool for a material scientist to understand what's going on with the material, and

there's been a lot of good work trying to correlate it with corrosion data, but I think the functional testing is most appropriate. And I think part of that reason why, too, is that the surface analysis is generally looking at relatively small areas of a device, compared to when you're doing a corrosion test, you're looking at the finished device, and so you can tell a lot more about the finished device doing that type of test.

DR. KRAMER-BROWN: This is Pamela from Abbott again.

Just one comment. Jack had a very good point, which is if you want to be able to look at the entire stent or device and be able to use it afterwards, that is where you get into the issues, and maybe that was the genesis of your question of have you observed any geometries that are problematic for characterization? I mean, you can always get around it, but it's usually a destructive way to get around it.

DR. LEMONS: And also, in post-implant analysis for retrieved devices, it's very much a problem to get those surfaces into a position where you can really truly characterize them. So, again, our experiments normally stop with environmental SEM where we can keep the voltage very low or keep them wet in the analyses we do. So it's a very powerful tool, but it does have its limitations.

MR. MOSKITO: As far as doing -- you can always use these analytic techniques to look at very specific areas. Even with XPS, where I mentioned the spot size in general is typically about 1 mm in diameter, we

can take that same instrument and do micro-XPS on a particular area so that you can bring it down to an analytic area of about a 20 µ diameter. So if there is a pit, if there is -- if you need to know the oxidation state of a defect, you can use XPS in small spot mode to gain that. It's a very specialized instrument, but it is capable of doing that.

DR. SCHROEDER: Something else that we have to keep in mind when we're going to techniques that maybe not everyone here even knows and you have to look up on Wikipedia is that they most likely have limitations, and we may not even fully know what the limitations are. They're probably semi-quantitative. As soon as you start sputtering, you're having matrix effects, and you're becoming even less quantitative. I think as soon as you dry it out, you no longer have the hydrated oxide forms.

There are all of these limitations that we're dealing with, and so I think that puts these into a realm of a certain place in the toolbox that we have available. So depending on how you want to characterize and how you want to think about your device.

DR. DI PRIMA: Well, based on the homework response where most of this is being performed out of the house of the people who responded, it was very obvious to us quickly that this wasn't quite as widespread as we thought. We have all sorts of really cool toys here at the FDA, and I think we run into the problem that we just assume you guys have them, too.

(Laughter.)

DR. LEMONS: To add one comment, in terms of metallics, it's very useful to do x-ray diffraction and glancing angle x-ray diffraction and now the micro techniques because we found that to be very valuable in analyzing phases in near-surface zones, especially where we have wear or some other type of feature.

So I think there are a number analytical techniques that are quite valuable that I'm not sure you would classify as imaging. But at least we found that to be extremely valuable in trying to understand, for example, in the cobalt alloy, any potential phase change at the surface where we have more acidic phase, the only way we've been able to get at that has been by the x-ray diffraction techniques.

MR. STORMENT: And we should remember, too, any of these techniques can be used with cross-sectional methodologies and with vibratory type of polishers. You can still maintain really high resolution, you know, submicron, deep on a nanometer scale. And then you can do these analytical techniques on the, you know, cross-section of the material that you're looking at.

DR. DI PRIMA: Well, thank you all for addressing that point, and hopefully we have a better understanding now of some of the challenges, and I guess we can always ask for some destructive testing.

So moving on to what hopefully will be a little bit more of an

interesting discussion, is there a general role for surface characterization in the process validation and/or monitoring? And this is sort of a lead-in to our second objective where someday, you know, would it be possible for us to just do surface characterization and then be able to know what the corrosion, let's say, properties of the device would be?

So this is where we're sort of moving, but just right now we want to know, should these techniques be more widespread?

DR. KONSTANTINO: I think that they're reasonable in the monitoring because changes in the surface may indicate potential changes in performance of the device. And so we're looking the surface and -- just to make sure nothing changed.

MR. STORMENT: Chris Storment.

With electrochemistry, we're looking at the broad reaction of that material to the environment. We're not going to be able to get that kind of information, you know, we're going to be looking at very small surface areas for surface analysis.

So to replace it, I don't think that's ever going to be possible. I think it's going to be as an analysis method that's going to be used initially, you know, to characterize what we have if we're starting off with a new material or a new process or if we have some sort of a process error or change that we're trying to analyze and understand. But we're still always going to use the electrochemistry because that really is what tells us the

global behavior.

DR. SAYLOR: Dave Saylor, FDA.

Maybe not replace, but say reduce. I mean, if we knew more about the relationships between, say, nickel leaching and some sort of statistical characterization of the surface, could you see, number one, rather doing the surface characterization of the nickel leaching and for that to be possible?

MR. STORMENT: Well, the problem with nickel leaching is it's leaching, and you're going to see all of the nickel, you know, you're not going to see that which leaches. So first of all, that's a bit of a problem. So nickel leaching in combination with surface analysis in combination with ASTM 2129, I think, really is the only way you're going to be able to get the entire picture.

DR. SAYLOR: Just to follow up real quick. I understand the entire picture, but I guess with more science, could you see doing more surface characterization relative to nickel leaching? I guess that was my question.

MR. STORMENT: I'd have to say probably not.

DR. KRAMER-BROWN: This is Pamela from Abbott.

I would just -- I'm sorry. Just, I have to agree with Chris on that. The issue with the surface analytical techniques is they measure one microcosm in the galaxy, that is, the device that's getting put in. And the

electrochemical techniques are giving you the overall picture.

And while corrosion happens on a little micro scale, it's just physically impossible to characterize the entire device to the point where you would know where that little microcosm might start to corrode or it might start to have a little bit of a different rest potential than another part. And then you get another device and it's totally different. And totally different, not necessarily from a processing perspective or an overall electrochemistry perspective, but just because within any material, you've got grain orientation and different grain size and structure and occlusion content and occlusion distribution. There are too many variables to take into effect.

So I hear what you're asking and I think it's a laudable goal, but I just don't think it's possible.

DR. KAMMER: I think it's also -- I mean, I understand the fact that people are saying that surface characterization tools are using, like, a very small spot size as compared to electrochemical techniques where the area is taken into consideration as large, that's very right. But I still think that it's very important that, for example, that small spot could be taken at, like, few spots, I mean, in order to get the better surface characterization of the sample, that's one thing.

And secondly, I think nickel -- as far as nickel leaching is concerned, I think it's -- I mean, if you do the surface characterization effectively, I think it can tell us a lot about the nickel leaching as well.

DR. DI PRIMA: Other thoughts, other comments?

I know that when we get data, there are often spectrums from multiple spots on a specific device, which does not give us the entire device characterization, but it can give us a sense of how consistent, you know, the oxide layer thickness is or how consistent your surface chemistry is, especially if you are able to get in and hit various geometries and actually get inside the crevices. So that's sort of, I guess, where our thoughts are going, but I don't want to go too far down that path because then Dave won't have anything to talk about.

So going back more to the process, like validation and monitoring, you know, would you be willing to measure your oxide thickness on like every 100th device, you know, every 50? Is it worth doing that, or once you have your technique established, are you set?

DR. CHOULES: Brian Choules.

I think we would have to first identify a real clinical problem to warrant such a level of scrutiny. If, you know, a device goes through DV testing and there's not an issue with nickel ion release and we don't change the process, you know, doing this level of characterization is just not necessary.

MR. SCUTTI: Yeah, I concur. You know, if we start to inspect in quality, we're going to be in trouble. The right way to do this, right when they manufacture products, is to find a manufacturing method that works,

lock down the processing variables, and go forward with having validated that manufacturing process with the initial data, such as might be supplemented by surface analytical techniques.

DR. DI PRIMA: Okay. If there are any further comments or questions for Objective 1, this is the time. If not, I will turn the floor over to Dave Saylor.

DR. BERG: Brian Berg, Boston Scientific.

These questions should be on the basis of risk; that's what we're after here is what's the risk to the patient? You know, without stating the risk assessment that's being done, there is no need to do an assessment.

DR. SAYLOR: All right. So for our second objective, we wanted to focus sort of what the perceived utility of surface characterization is -- I think we got a good hint of that from the discussion we just had -- as well as looking forward, what we could do with this in 5, 10 years, which we also started to talk a little bit about.

So our specific objectives were to discuss the relevance and utility of surface characterization, what we know about surface structure-property relations, and any potential criteria for either desirable or undesirable surfaces.

So the first homework question we asked related to this objective was have you observed or identified any structure-property relations? Most people said no; a handful of yeses who pointed to some of

the nitinol results that have been reported in the open literature that focused mainly on thermal oxides for nitinol.

The second question was should there be an acceptance criteria for oxide thickness and chemistry? And this was fairly overwhelming no; a couple of yeses. And actually, specifics were given for nitinol in terms of the oxide thickness and chemistries, so I've just listed them there. You can see less than 15 nm, no nickel-rich phases. Another one was less than 50 nm, less than 20 at% nickel-rich regions. And one of the noes suggested, as a guideline, nitinol, the oxide thickness should be less than 10 nm.

Sort of the common responses for why acceptance criteria weren't appropriate for the surface characterization, the first was that there aren't established structure-property relations, which went to my question that there's no way to go from anything you observed. In general, there's no way to go from observed surface structure to any performance, either in vitro or in vivo. As it was pointed out, you're only looking at a small fraction of the total surface area. The available techniques are not adequate, and this was things like the sputtering is compared to silicon oxide and not really titania. And, sort of, doing the corrosion and nickel leach testing are, in general, easier and a more direct measurement than looking at a few small areas of the surface.

So I have two discussion topics on these. The first was if we just sort of took acceptance criteria out of this, it's not practical, it's not

feasible, are there examples of exclusion criteria that would be? In other words, we can't say that you have to be better than this. We can say you can be no worse than this. You know, sort of along those lines, what are desirable features or what are undesirable features in the oxide layer? So I'd like to open that up for comment, discussion.

(Laughter.)

DR. SAYLOR: I guess if you were -- oh, I'm sorry. Thank you.

DR. SCHROEDER: I guess I'll start at a general place, but for stainless steels, you expect a certain concentration of chromium in the oxide layer, so you could look at that as -- I don't know if we're making it an acceptance criterion, but an expectation would be a certain concentration of chromium, and in nitinol, you're expecting a certain concentration of titanium in the oxide layer, so that, again, would be an expectation.

Yeah, I think a lot of us use electropolish. I think that came out in the results. There have been examples of thermal oxides maybe not being that great, but I still seem to see them on devices.

So if you were to set up an acceptance criterion or an expectation around oxide thickness that was based on you really want to use electropolish devices, I would say if that's the FDA's expectation, you should be more direct and say use electropolishing as opposed to kind of backing in a thickness requirement. So that's kind of general thoughts on what you could get out and use as an exclusion criterion.

DR. SAYLOR: You're saying based on processing and not results, not thickness, for example?

DR. SCHROEDER: I think the thickness would be secondary. I mean, if you're really focused on thickness, that's probably because you want to exclude thermal oxides, I would assume.

DR. SAYLOR: I mean, I don't think we want to exclude anything. In the end, we don't really -- it doesn't matter how you process it as long as you can demonstrate that it's adequately resistant to corrosion and performs well in vivo.

DR. SCHROEDER: And that's what brings us back to the functional relationship to the results, so yeah.

MR. MOSKITO: I can't really give a recommendation for this particular industry, but as an example, we do a series of tests on stainless steel, 316 stainless steel, for the semiconductor industry for the insides of stainless steel tubes for gas delivery systems.

In that case, there are three techniques: SEM to look for stringers and occlusions on the surface of the material; there is XPS used to look for the oxide states and the ratio of chromium oxide to iron oxide on the surface; and then there's an auger component also that measures the oxide layer thickness and the carbon concentration on the surface. And there are very specific cutoff points for all of those different parts of the surface that are looked at in those three different techniques.

So even though I can't say whether that's needed here, but it is used in other industries. And this is under SEMATECH.

DR. SAYLOR: I guess a lot of folks mentioned that they actually, you know, did this characterization during R&D and I think it's maybe analogous what Erica asked with the corrosion. I mean, at what point in your process is there any specific characteristics of the surface that you see, at which point, now I have to -- it sort of leads you to believe you need to make a change or -- okay.

DR. KRAMER-BROWN: So this is Pamela from Abbott.

I wouldn't say that the results led us to say that we needed to make a change because by the time we did that full surface characterization analysis, it was to find out what we had there because we already knew it worked well, we had a lot of data.

And so in the interest of fully characterizing the device and fully understanding what we want to implant in patients, we do this test as an internal test for us to just see what's there, make sure we know what's there, but we do not use it as -- it's not used -- what's the word I want to say? It's not an acceptance criteria; it's information. We gather a lot of information during the R&D phase about the material and the device to fully understand it so that we can pass the red face test and we know that we're doing the right thing for the patient.

So what would bring up, you know, an alarm button? Probably

if we didn't see any oxygen on the surface would bring it up. I'd say hey, why is this performing so -- and then it would be why is this performing real well and there's no oxygen on the surface?

DR. BERG: Brian Berg.

Just to comment on one of the uses of SEM that we all use it and we haven't stated here is to look for occlusions. It's part of the alloy characterization. So I guess, perhaps, if I didn't say that we use SEM for submission purposes, that would be remiss because of that aspect of the value of occlusion. And, of course, we know occlusions are a big factor in corrosion as well.

So there is some use for it, just that, for the most part, for the corrosion issue, it looks very specific and it's not a functional test. I mean, you have to do theoretical relationships or other derived relationships to go from the measured values under the as analytical techniques to what the practical and functional value of it is, and so we trust the functional value.

DR. SCHROEDER: I would just say another example, from an R&D perspective, is you get a functional result that's not what you expected. You go back, you look at your process, and I'm not just talking about the electropolishing, but the full downstream processing, loading into the delivery system, all of that; identify what you might think is the cause, and then you pick a technique and you pick areas on the sample for control and for comparison based on that, see if that gives you anything, go back, try and

change the process, look again. So that's an R&D example that I would use, as well as I agree with Pamela as kind of the final, we know this is good, let's do a characterization at the end.

DR. MEGREMIS: Yeah, just to back up a little bit to what Jack was talking about with dental alloys earlier. For corrosion testing of dental alloys, one of the simple tests they do is a static immersion test for seven days, and one of the things you do is you collect solution after one, three, and seven days. And one of the things you see is for certain alloys, like cobalt-chrome alloys, it drops the first day.

If you collect the solution and look at it, it's relatively -- it has a relatively high ion content and then it goes away. And that's because once you put it in solution, the oxide thickens, in most cases, depending on what solution you put it in. So that again gets into this whole thing, if you look at oxide layer thickness of just something taken off the shelf and prepared, it's going to probably, depending on the application, be a lot different than the thickness that you see in vivo.

DR. SAYLOR: Okay. I guess we're going to move on. We already sort of started to address the Number 2 point here, which sort of goes with what I was trying to get at earlier. If we knew more about how the surface structure -- what the surface structure-property relations were for, say, nitinol or anything else, are there benefits to establishing that and, again, is there any way -- and there was some varying opinion about that -- to sort

of replace the need for some test with surface characterization?

But maybe we can have some comments directly addressing, you know, what better establishing these relationships would bias, if anything, in the future?

DR. BERG: Brian Berg.

If you know what the right structure is for your optimal biological response, that's awesome because then you know what to target your processing to achieve. But, normally, the way you get there is you develop processes and then you see if they work well. I mean, yes, if we know what an optimal process is, then we can -- I mean, know what an optimal endpoint is, that's very helpful.

DR. EISELSTEIN: Hi, this is Larry Eiselstein from Exponent.

I think Brian sort of put his finger on the reason why I'm getting the impression that most people believe that the structure-property relationship in detailed compositional analysis isn't likely to be too successful. One way to look at it is both the corrosion properties and the strength properties, say, like fatigue/strength properties, depend on, really, the weakest link in the surface that you're looking at. And that's one of the reasons why the distribution of breakdown potentials is so variable is that the whole surface isn't breaking down; it's the weakest link. And as a result of that, you do the statistics but, you know, generally you sort of expect a Weibull distribution or a lognormal type of distribution on those values. In

some cases it might not be that bad.

And the problem with the surface technique is that, you know, you can look at two or three spots, but that isn't really where the device is going to fail, necessarily. It could be that it's at the -- fatigue, for example, you would expect that the fatigue failure would probably occur at the maximum, you know, occlusion that happens to be in the volume of the material that you're looking at. Somebody had mentioned earlier, the smaller the wires get, the more likely that that's going to be a problem; that's certainly true.

Same thing with corrosion is that you have, potentially, an occlusion that's surface intercepting; that might be a very rare event, but the chances you're going to be able to pick that up in an auger or ESCA analysis is pretty minor.

So I think that that's possibly one of the reasons why this is, I think, hard for the practitioners and the manufacturers to think that, you know, knowing more, even in the future, is likely going to help a whole lot.

DR. SAYLOR: Actually, I think when we actually developed this question, we were thinking more along the lines of nickel leaching and not necessarily the pitting/crevice corrosion, which is more of a sort of general surface-mediated property.

DR. EISELSTEIN: Certainly, you know, you might have a little bit more luck, I would agree, with nickel leaching, you know, if you do your auger

and see that, you know, everywhere you look, you have 80% nickel concentration, then you might think you have a problem. But I'm not sure enough testing has been done yet to show what that relationship would look like, and the amount of work that that might take could be quite substantial.

DR. ROSENBLOOM: Shari Rosenbloom, Corrosion Testing Labs.

I agree with what Brian said and what Larry said about using this kind of a characterization. With regards to the nickel leaching, you know, I agree because nickel leaching is more of a general phenomena as opposed to localized, like pitting, that this might provide a way of -- if we knew what the -- if we could characterize a surface and understand how that might relate to nickel leaching, maybe you'd have a shot at getting somewhere.

The problem that I would think is at what cost and, you know, it's an expensive test, and would the actual in vitro testing that we currently do, does that provide enough data anyway? Does it give you what you need a little bit easier, a little bit less expensively?

And the other thing is just that because nickel leaching is a time-dependent phenomenon and because the surface is reacting to being in solution and the oxide is changing with time, I wonder how you might be able to account for that by just simply understanding the oxide in a given moment.

DR. TAKAI: Sorry, I'm not on the panel, but I wanted to ask a question. So I wanted to give a little background on why this question about surface characterization and, you know, whether or not we think there's a

role in it and wanting to hear from everybody what people's thoughts are, so we've encountered situations where we have device submissions for nitinol devices and the manufacturer tells us oh, we don't do any surface processing on our devices, just as manufactured, and then we get corrosion testing, the F2129 testing, done and then we get values that are, according to the Corbett paper, it would be in the poor category.

Then, if there is no other testing performed, then we have this question of, well, then, what kind of assessment should we be asking for? The device could be perfectly fine, but, you know, what kinds of assessments do we need to assess that type of situation?

And now, so we know from the literature that certain properties of surface oxides on nitinol, for example -- and I think there have been references that said something in the order of 50 nm to 100 nm and thicker might be problematic in terms of corrosion and possibly nickel leach testing, and having nickel-rich regions obviously raises a concern that you may have a nickel release subsequently.

Now, immersion tests to look for nickel release could be a lengthy test. You know, the question we don't exactly know the answer to either is how long of a test do you really need to do for nickel leach testing. But we're thinking that perhaps, you know, if you could do the surface characterization test in a relatively shorter period of time compared to a lengthier nickel release test, would that augment or possibly replace some of

the lengthier other assessments? So that's where we were coming from.

DR. SCHROEDER: I'll add a comment to that, as far as what your expectation might be if it's -- I think if someone has prepared the surface and then created a thermal oxide, you might expect a thicker thermal oxide. If someone's really going through all manufacturing processes, including shape setting without doing anything to the surface, I'd expect additional contaminant elements.

So you would be picking up things that weren't the nickel, the titanium, the oxygen in kind of a range. And that might be something to look for and might be something to be concerned about if you want to separate that condition from a thermal oxide that was prepared after cleaning your surface.

DR. LEMONS: Completing a textbook at this time, we, biocompatibility and biomaterials, the central issue is in the evaluations, one evaluates physical, mechanical, chemical, electrical, and biological properties of surgical implant biomaterials. Okay, if we take the subset of that and ask the questions about structure versus property relationships and then go further to say, you know, if we say the surface structure versus property relationships, you only gain data on certain specific properties dealing with the surface characterization per se.

However, as we're looking forward, we've seen a number of studies and a number of activities where surfaces are modified very

specifically, chemically, to make a claim or to do something that's unique to the application. The one we were involved with is a sol-gel technique to result in a very highly pure surface that would change tissue integration.

Okay, there you have something that I think needs to be tested for, for consistency. But if you go back and look at the literature in terms of processing metallics, and the experience that we have, I don't know that you're going to gain substantial information unless there's some question about the alteration of surface properties and products that are in the commercial market or coming available in the commercial market.

But I think the analytical techniques to gain informational and surface properties is just one of the many tools to qualify. And we're really talking about quality control and analysis, I'm assuming, and there's regular, you know, techniques for sampling that are routine to the industry that are applied now. And I'm not sure how much you want to go beyond that for quality products.

DR. McLUCAS: Emily McLucas.

I think if you review the literature, there is very good correlation between nickel content in the oxide layer and nickel leaching. I think, as somebody alluded to earlier, the biggest drawback with different techniques like XPS is that the area that you're analyzing is so small that by the time you actually analyze a meaningful area, it would be easier to do the nickel leaching test in a lot of instances.

MR. LASLEY: Yeah, I agree with that as well. This is Chris Lasley. I know Christine Trepanier and others have done reports on oxide layer thicknesses by using different heat treats on electropolish material and establishing a correlation between oxide thickness and breakdown potentials, showing that there is some drop after about 50 nm, I think, and more significantly reductions in breakdown potentials after like 100 nm, and I think they even had stuff like 1000, 10,000 nm in those studies with very severe heat treatments.

So those testings, they're really trying to correlate the surface oxide with the more functional parameter of breakdown potential in this case. And I think it's more appropriate to look at that functional number as opposed to trying to look only at the surface thickness. And even better yet, it's more important to look at the clinical results that might represent certain oxides rather than just the F2129 breakdown potentials.

DR. SAYLOR: Yeah, I don't think we were -- I think our main thought in developing this question was the nickel leach because it is such an onerous test and could that replace it. But the comments seem to be it's almost better to do the nickel leaching. Okay.

DR. ROSENBLOOM: Shari Rosenbloom.

I wanted just to get back to your question, Erica, about the potential submission with what would be possibly characterized as poor F2129 performance, and then you're saying, so what else should we do and

should we do the surface characterization?

You know, I think that certainly when F2129 shows behavior that we're not sure or you're not sure about, then it's good to do other tests, and I think that was the whole point that Rick was making when he made the three categories of acceptance, you know, poor, moderate, and acceptable, was to say that if it's in a moderate range, say, that we should look at more things. And certainly if it's in what he considered the poor range, you'd absolutely have to look at more.

And the question is, of course, how do we understand truly what this gives us in terms of the clinical performance? What does this really tell us that other methods might not tell us? And I think that some of the pushback that you might be feeling or we're sort of feeling in the room today about the use of this test is coming because I'm getting clients, for example, that call me that have very good F2129 performance and they're saying but, you know, we're afraid FDA is going to ask us to do this, this is going to become do we have to do it, is it going to become a standard test, and it's expensive and it's -- and yet, all of our data shows that it's good and maybe that's a very different situation from what you just asked about the sort of poor to marginal device.

DR. TAKAI: So I think we've seen devices across the spectrum, and I want to note that the situation of having a non-surface treated nitinol device with marginal or poor F2129 results happens in more than one or two

submissions, so it's something that we have faced a number of times.

And on the flip side, you know, we don't think we can hang our hat completely on just the F2129 test. So then the question becomes, well, what other assessments should perhaps be considered on a more routine basis?

Thank you.

DR. ROSENBLOOM: Can I just follow up? And I guess this is true with all of these tests, but until we truly understand what the correlation is between the result of the test and the performance in vivo, you know, it's very difficult.

MR. STORMENT: Okay. Yeah, a case in point. We have a number of explant data that show that even for marginally performing, so-called marginal performing parts, we do not see any visible signs on these explants of any corrosion, and we've done this on 400 or more samples for a particular implant. So it's difficult to, you know, say everything has got to be on this specific number because there is obviously more at play.

DR. LEMONS: I would just simply make the comment from a research and development standpoint. I think there is a reason to better understand. And if we're talking about nickel leaching, I would normally associate that with elemental nickel being transported. Now, if we're talking about electrochemical corrosion and we're talking about the preferential loss of nickel as an ion species, that becomes very critical in terms of the grain

boundary structure, the oxide structure, and the characteristics of the material.

So if one had established relationships to biocompatibility, it might be worthwhile to have another analytical technique. But at least, as far as I understand the nickel-titanium today, that is not the case for most of the products unless there is something unusual that is happening here.

But if the claim is, for example, in the titanium oxide, that you're going to have one of the phases there, you're not going to have the triphasic material and you're going to have TiO_2 only and the other is excluded, the only way you're going to be able to prove that on a routine basis is with one of the analytical imaging techniques.

So it depends upon what the particular question is that one hopes to answer, you know, with regard to studying the surface properties.

DR. KONSTANTINO: I just want to mention, I doubt that without any surface treatment they will have a clean oxide layer. I just don't see it happening. On different surface treatment, we did explore corrosion on ex vivo units of the animal studies in 90, sometimes 180 days, when we developed implant.

So I don't think it's something that people -- I assume other people are doing it and -- do it, you're doing the animal studies, anyway, you can add a little bit more. So something to consider.

MR. MOSKITO: Just a last comment. If there was ever found a

correlation between a surface effect and corrosion and nickel leaching -- you know, it doesn't have to be auger, it doesn't have to XPS. There are dozens of different analytical techniques that can look at that surface. And if you can find a correlation, it can be measured.

I'm a big fan of surface characterization, obviously, but you tell me what you're looking for, and I can probably figure out how to get it. It doesn't have to be the techniques we're currently using, but if you give me a correlation, it can probably be done.

DR. SAYLOR: Okay, if there are no further questions from the panel or comments, we have about 10 minutes left, so if there are any questions from the audience for the panel at this point, we will entertain those.

(No response.)

DR. SAYLOR: So if there are no questions, I think we're going to conclude for the day. I'd like to thank everybody for coming and John for stepping in. And tomorrow, we are going to start at 9:00 a.m. with nickel leach talks.

So thanks again, everybody.

(Whereupon, at 4:50 p.m., the meeting was adjourned, to reconvene the next day, March 9, 2012, at 9:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CARDIOVASCULAR METALLIC IMPLANTS: CORROSION, SURFACE CHARACTERIZATION, AND NICKEL LEACHING

March 8, 2012

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health.

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CATHY BELKA

Official Reporter